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THE DIFFERENTIATION AND TREATMENT OF THE COMMONER FORMS OF NEPHRITIS

ABOUT twenty-five years ago studies in nephritis began to be predominantly physiologic in point of view in contrast to the studies of the nineteenth century which were largely anatomic. This logical change in point of view was influenced considerably by Strauss in 1902, later by Schlayer, and in this country received a tremendous impetus from the methods of analysis elaborated by Folin.

The experimental method of approach to problems along with fairly adequate chemical methods of analyses of body fluids excited high hopes for most refined diagnosis of renal disease which is best exemplified in the work of Schlayer, who endeavored, it will be recalled, to determine whether the lesion in any specific case of nephritis affected chiefly the glomerulus, the tubule, or the arterioles.

While these endeavors led to disappointing results in the clinic, nevertheless it was distinctly worthwhile to have had the problem of renal excretion clearly defined and probably this precision of statement was a large factor in inciting a reexamination of the question of mode of renal activity in health. But a by-product of the experimental and physiologic point of view was less fortunate in that it tempted investigators to formulate classifications, classifications which were useful primarily to the student in the course of a research, but leaked out

of the laboratory prematurely and were accepted by the uncritical as newly discovered accessions to knowledge.

Possibly the worst feature of classifications of a disease is not so much that they are rigid, dogmatic, and lose touch with actuality, but rather that one classification produces another until the end is hopeless confusion. This, to many, has been the result of classifications of nephritis. As a reaction to numerous futile attempts, it has even been suggested that in the main only two types of nephritis are clinically recognizable; acute and chronic. Even if one be disposed to accept this, might it not be suggested that when acute nephritis fails to subside but is prolonged into months or years and finally terminates life, the division between acute and chronic is purely arbitrary and reflects no *sudden* transition in either renal function or renal pathology? Moreover, if the careful studies of the last decade in particular have revealed anything it is: That the disease we call nephritis is not restricted and confined to the kidneys; rather it is profound disorder affecting remote and apparently unrelated tissues, even the bone-marrow.

It seems to me very important to emphasize the incompleteness of our knowledge as I have done, because the idea is too generally accepted that differentiations of a disease into types and classes represents a refinement of knowledge rather than the purely hypothetic groupings for convenience in study which they should mean. Our knowledge of the disease of an organ whose mode of function, whether simple filtration or active secretion, is still open to debate and, unproved, can hardly have arrived at a stage where classification is definite and final.

The best defined of the clinical types of nephritis is the acute form which follows infections and is produced either by bacteria or by bacterial toxins. The onset, often abrupt, during convalescence from the primary disease (tonsillitis, pneumonia, scarlet fever, et al.) resembles in some features an acute disease. There are often fever and headaches. The urine is smoky or bloody, then scanty, and in severe cases there may be anuria; some edema is always present and there may be anasarca. In carefully studied cases there is notable a considerable elevation

of blood-pressure during the height of the disease with corresponding retention of nitrogen in the blood (high non-protein nitrogen and urea nitrogen). Convulsions and transient blindness are common. Then all symptoms and signs abate rather rapidly so that in a week the patient is desirous of being up. Albuminuria is, however, apt to persist for some time even in those cases that make a perfect recovery. In well-developed cases the disease is unmistakable, but I am led to believe that milder forms are often overlooked, neglected, and progress insidiously into chronic and fatal nephritis.

We commonly think of acute nephritis as a complication of scarlet fever, but it is much more often a sequel to acute tonsillitis. When the temperature has fallen to normal and the throat is sufficiently healed so that the patient can eat we usually think convalescence established, and our attention to the patient no longer necessary. How often, I wonder, is the urine tested after the patient has left the bed? The indication for this is definite since nephritis usually develops from ten days to two weeks after the tonsillar infection. Only by meticulous attention to seemingly unnecessary details can mild cases of acute nephritis be detected, proper treatment carried out, and permanent damage be prevented. Why is it that the mild cases of some severe diseases have such an ominous reputation, ambulatory typhoid, for example, and it has often been remarked that it is the mild cases of scarlet fever which are more apt to be followed by complications and sequelæ such as nephritis. The reason probably is that the milder cases are not so well protected, they do not go to bed, or they remain in bed an insufficient period. I am convinced from experience that many cases of incurable nephritis might be prevented if we watched the urine as carefully as we watch the thermometer.

I have but little to say regarding the treatment of acute nephritis and my opinion will be held as heresy by many. If the patient be kept in bed, and treated in general as an acute infection it is of minor importance whether the diet be low in protein and salt or not. Experience of several generations advocates a milk diet which is neither low in protein nor low in

salt. The opportunity once came to me to treat a considerable number of cases of scarlatinal nephritis by various diets. I was not able to distinguish any clear-cut influence of food in the course of the disease. It may well be that when the period of acute nephritis is protracted, and edema or nitrogen retention persist unduly, special indications arise. This is probable; it is also exceptional.

But acute nephritis does not invariably go on to recovery, it may progress into a chronic disease lasting years. Then there may be, often there is, a subsidence of all of the more *striking* symptoms, only albuminuria persists. The patient considers himself well, since he feels well. One of the reasons for some of the conflicts of opinion concerning problems in nephritis is that it only seldom happens that a single physician has the opportunity to observe one of these protracted cases during the whole course of the disease. Each of us is apt to see a period which demarks some episode, we seldom see the whole.

Then there is another type of nephritis of less abrupt onset, although in some instances it might be properly called acute, which I wish to refer to, not because it is common, but rather because there is considerable confusion about it. Nephrosis is relatively a new name and the term refers to the disease formerly called parenchymatous nephritis, only that our knowledge today is a little more detailed and possibly a little more exact. Whatever the clinical designation, nephrosis or parenchymatous nephritis, the large white kidney is often the conspicuous pathologic lesion. The most obvious clinical features are edema, albuminuria, and a decreased urine output. Followers of Widal point to the scant chlorid excretion as significant. There may or may not be an increased chlorid concentration in the body fluids; this depends on whether much or little water be retained proportionate to the chlorid retention. There is also a conspicuously high concentration of cholestrol in the blood, the significance of which is obscure, and the basal metabolism is often as much as 25 or 30 per cent. below normal. Think of a pale, water-sodden boy with marked albuminuria and you visage the picture. Some signs often noted in other types of nephritis are not found in

pure nephrosis. For example, the blood-pressure is never elevated, there is never albuminuric retinitis, nitrogen retention in the blood, or blood in the urine. In brief, those disturbances of function which seem likely due to glomerular lesions are absent in nephrosis, which is more particularly a tubular degeneration. But one must hasten to add that cases are not rare in which the evidence indicates both a glomerular and a tubular lesion.

There is now a boy in the ward at the New York Hospital who presents all of the typical features of nephrosis, generalized edema, albuminuria, high cholestrol content of the blood, and depressed basal metabolism, but in addition the urine contains red blood-cells, the urea content of the blood is persistently above normal and the blood-pressure is elevated. These mixed types are possibly more common than the pure classic variety and these cases are the despair of a devotee to any rigid system of classification. Actually there is no difficulty in regarding those cases as examples of disease of both glomerulus and tubule, or in the Widal system defects of both salt and nitrogen excretion. The real difficulty is that no matter how we regard the kidney lesion, the essential factor back of the renal disorder is completely obscure, and until we know that our debate concerns a minor detail. The vascular lesions exemplified in the glomerular tuft involve the whole vascular system (note the lesions in the retina), and the conspicuous edema is not due to a lesion in the renal tubules but is a result of some change in the colloids in all the tissues of the body, a change which causes the colloids to imbibe and retain water.

So in our treatment we are not so much rational as we like to think. Some measures have been found to be useful and we rationalize about them. Because there is a considerable loss of albumin in the urine it has been suggested that it is better to feed patients suffering from nephrosis with liberal amounts of protein. And on this sort of diet some of these patients improve, but it seems to me quite as likely that the liberal diet is operative in aiding the organism to overcome an obscure infection as merely by restoring depleted protein stores. The depressed basal metabolism in these cases is also a mysterious affair.

Feeding thyroid may sometimes be of benefit; not always. In the case of one patient whom I had opportunity to study over a considerable period there were rises in the basal metabolism from −30 to normal and recessions again like successive waves uninfluenced by very liberal thyroid treatment during the whole time. It has been long known that thyroid administration has some influence in mobilizing body fluids, in ascites, for example; but the point here is that it is by no means a specific therapeutic agent in nephrosis. So far as my observation goes, neither high-protein diet nor thyroid has any influence on the albuminuria of nephrosis and I take that sign to be indicative of the persistence of the primary basic disease, be it infection or some other factor. Here I wish to sound a warning concerning treatment in cases of nephrosis. Before attempting to carry out the orthodox high-protein feeding be very sure that the patient is fully able to excrete the products of protein catabolism, the urea, and other ingredients of non-protein nitrogen. If there is already some elevation of the urea in the blood, or if there is vascular hypertension, or delayed phenolsulphonephthalein excretion, then difficulty can be predicted. But I have seen many cases presenting no evidence of nitrogen retention on the low diets so commonly used. When the blood analysis in the case of a patient on a low diet is normal it is *not* safe to assume that the nitrogen waste from a high-protein diet will be easily excreted. Convulsive uremia may occur and the blood analysis then indicate that there has been a rapid nitrogen retention. The only rational way is to prevent mistakes by analyses of the blood at regular intervals, rather than to proceed boldly on assumptions.

In contrast to the high percentage of recoveries that some internists have noted in nephrosis my own experience has been discouraging. I have not yet seen one case restored to normal health. The edema may subside and severe albuminuria persist. Some progress to typical chronic nephritis with hypertension. Some succumb to acute infections of which, curiously, pneumococcus peritonitis is the most common.

The most common form of nephritis is the chronic type. It is one of the chief causes of death in America and in the metro-

politan district this disease ranks seventh. There are now some 40,000 persons living in this city who have chronic nephritis. In the later stages of the malady chronic nephritis is one of the easiest diseases to recognize. The facies alone are often characteristic. But it is usually a disease of long duration, years may elapse before the advent of subjective symptoms and in the early period, before renal elements are replaced by connective tissue and the kidney is reduced to half its normal size, diagnosis is often very difficult. And it is this early period when treatment, if ever of any use, promises most. When glomeruli and tubules are destroyed there is no replacing them.

The problem of early diagnosis is best exemplified in men who are refused life insurance because of albuminuria. The patient may look in prime health, and he usually has no symptom of disease. Examination reveals nothing, even the blood-pressure may be normal, though it is often on the borderline. It has been the common habit of the profession to take these cases rather lightly, and various meaningless names are in general use—accidental albuminuria, physiologic or simple albuminuria—but albuminuria is never a sign of sound health and the life insurance companies have learned that these patients die before their time. In persons over thirty-five years of age, showing a trace of albumin in the urine, the death-rate from nephritis is three times the normal. This fact is significant but, at the same time, the diagnosis of nephritis cannot be made on albuminuria alone. It is hardly a safe diagnosis when there are also casts, unless there is some supporting evidence. Hence a confusing number of functional tests have been advanced from time to time in the hope of making diagnoses more precise. After years of careful work with all kinds of tests I am forced to conclude that nearly all of them are useless in the study of early cases. In the late cases when it is seldom a question so much of the identity of the disease as it is of the extent of the involvement, various tests are of some help. But it is well to remember that no test exists today sufficiently delicate to indicate faulty renal function in a person who has

been deprived of one kidney. In other words, more than half the glomeruli and tubules must be destroyed before renal impairment threatens. In practice I have been more impressed by information yielded by the simple concentration test of Addis, and the water excretion test of Strauss, than by the elaborate and irksome studies often advocated. When a person is deprived of all liquid (except that in his food) for twenty-four hours he will normally excrete a concentrated urine; specific gravity rises gradually to 1.026, 1.028, even to 1.034. If the highest concentration attainable under these conditions is 1.024, or 1.022, it is highly probable that definite renal disease exists.

But concerning the early period of chronic nephritis the diagnosis is often in doubt, at most only probability is attainable. At a later period careful consideration of the results of thorough examination reduces error to a very low percentage.

The treatment of chronic nephritis in my opinion is usually futile. We are not certain of the cause of the disease, although there is evidence pointing to the persistence of infection as a cause. But even when we accept this hypothesis in individual cases it is only now and then that an infection can be localized (tonsils, sinus, etc.), and even less frequently can the infection be cured. Of cures I have seen very few instances even when the attempt was made at an early promising period of the disease. In the vast majority of cases the disease is insidiously and relentlessly progressive.

Under these circumstances treatment is restricted to palliative adjustments. It is probably prudent to decrease the demands on a diseased organ before the advent of symptoms caused by incompetence of the organ. But the average patient will not consistently follow this advice until some episode occurs indicating its necessity. Only the exceptional man will bother to watch his protein and salt intake while he feels quite fit. He may for a while, but not for years.

At the late period in the disease, when there are symptoms due to nitrogen retention, and to vascular disease, various measures, such as highly abnormal diets and copious water drinking,

often produce very gratifying results in the laboratory reports, and quite likely they may prolong life. But I am not convinced that the continuation of existence which is useless to the patient, devoid of pleasure and of participation in life's activities, is a kindness to the patient and certainly no matter for pride to the physician.

CLINIC OF DR. ARTHUR L. HOLLAND

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THE GALL-BLADDER FUNCTION AS AFFECTED BY THE OPERATION OF GASTRO-ENTEROSTOMY

THE operation of gastro-enterostomy as performed by experienced abdominal surgeons is a relatively simple surgical procedure and it appears to meet the requirements in many of the cases in which it is specifically indicated, but in not all of these.

It appears to be most efficacious in ulcers of the pars pylorica, particularly duodenal ulcers, where there can be demonstrated some degree of obstruction.

In my experience the results have been best in indurated duodenal ulcer cases in which the signs and symptoms have been those of a beginning decompensation of the stomach. I have always felt that any lesion on the gastric side of the pylorus should be excised, not that such an ulcer might degenerate later into a neoplasm, but because one can never be quite sure if such a lesion in the stomach is a simple ulcer or a malignant process. I will not attempt to compare the results of other forms of surgical treatment, such as subtotal gastrectomy and other plastic operations.

It has been repeatedly pointed out that the operation of gastro-enterostomy is not planned with due regard to known physiologic laws and that while it may prove instrumental in the actual healing of an ulcer the transgressions on these physiologic laws may and often do cause symptoms that in no way relate to the original disease.

To understand the failures following this procedure, apart from those due to faulty technic, early closure of the stoma,

vicious circle, jejunal ulcer, and secondary adhesions, one must think of the disturbed mechanico-dynamic conditions in all three parts of the duodenum which make up most of the proximal loop.

We know that abdominal comfort depends largely upon a fine adjustment of the tension within the gastro-intestinal tube—an increase over the normal for a given section of the tube will result in pain or some discomfort and a lowering of tension may also give rise to symptoms. In the stomach and those portions of the tube proximal to it, a release of tension usually makes itself apparent as nausea.

In the small intestine tension is highest in the duodenum and gradually diminishes down to the terminal ileum. A vent, as provided by a gastro-enterostomy stoma, may result in a release of tension in the duodenum, or a kinking at the stoma, brought about by peristaltic waves in the stomach pulling up this part, may cause alternately an increase and decrease in tension. Pain, pressure sensations, nausea, and most of those symptoms that the patients complain of who have been thus treated can be reconciled to this imbalance of duodenal tension.

A stomach or duodenum embarrassed by a Harris band or a simple adhesion often complains in exaggerated symptoms. How much greater must be the embarrassment of the attachment of a heavy loop of squirming intestine to the fundus. Symptoms are undoubtedly thus caused.

These are not new thoughts, but they are not considered as often as they should be by those who would indiscriminately employ gastro-enterostomy in the treating of these gastric and duodenal lesions.

In the Surgical Follow-up Clinic at the New York Hospital, it is my privilege to examine a large number of patients who have been subjected to surgical treatment for ulcer. I have been struck by the large number who state that their regular ulcer symptoms have been relieved by a gastro-enterostomy but who continue to have indigestion of one kind or another, and in most of these we can, by careful *x*-ray studies, find no reason for the symptoms, no evidence of stasis, adhesions,

marginal ulcer, etc. It is interesting to note that this indefinite indigestion complained of is not infrequently similar to that which we find associated with cholecystitis of a mild type, and yet we know that at the operation the surgeon has usually found the gall-bladder to be apparently normal.

It has occurred to me, as it probably has to many others, that a disturbed physiologic sequence might in such cases have caused a dysfunction of the gall-bladder sufficient to explain some of this indigestion.

This brings us to that most absorbingly interesting subject of gall-bladder control.

Despite the extensive experimentation that the physiologists have indulged in, we can as yet not say definitely what force or agent or agents operate to cause a gall-bladder to empty.

I gather from my reading of the recent and near-recent literature on this subject, that the largest number of experimenters conclude tentatively, at least, that this emptying is dependent on chemical action rather than upon neural control through reflexes and that such chemical agents reach the gall-bladder or its control center by way of the blood-supply rather than through its effect on the duodenal membrane.

If I were sure of this I would go no further in this speculation, but I do not believe that we are as yet in a position to say that neural impulses started in an antrum, pylorus, or duodenum do not play an important part here or that differences in intertubular tension can be excluded as exciting causes of gall-bladder emptying. With this thought in mind, I have begun to have examined, cholecystographically, patients who have had a gastro-enterostomy performed.

Dr. Belden, director of the *x*-ray laboratory at the New York Hospital, is collaborating with us in this investigation.

We have as yet had only eight such patients thus examined. In all but two of them either the gall-bladder failed to accept the dye or, filling normally, it failed to empty within the time limits that have come to be regarded as normal. In none of these cases was there any evidence to suggest the possibility of adhesions involving the gall-bladder. The two patients whose

gall-bladders appeared to function normally reported freedom from symptoms. All of the others had some complaints to make—mostly of more or less constant vague indigestion.

One must not forget that cholecystitis is often associated with peptic ulcer and that this coincident or concomitant disease may cause some of the indigestion that the ulcer patient suffers from. It will, however, usually be found that these are the cases in which the ulcer syndrome is not well defined, but which can be classed as of the irregular type. In all of these cases reported, the histories are of the regular type, the patients having been operated upon for obstructing duodenal ulcer. As I have already mentioned, the surgeons have reported in each case that the gall-bladder at the time of operation was found to be apparently normal.

It should be pointed out that as yet we cannot depend absolutely on the Graham test. It has, however, been so very helpful in practical diagnosis that we cannot afford to ignore its findings, particularly when supported by clinical findings and a suggestive history.

An interesting phase in this speculation is, how much pain or other symptoms can a gall-bladder that is functionally abnormal cause, and how?

Should it be proved that this operation may be responsible for gall-bladder dysfunction, would we be justified at the time of the operation, in removing the gall-bladder, when possible without unduly increasing the risk, hoping that we might thus prevent some of the discomfort that so frequently follows this operation of gastro-enterostomy?

CLINIC OF DR. BÉLA SCHICK

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TUBERCULOSIS IN CHILDHOOD*

As you know, most of the pediatricians maintain that tuberculous infection usually takes place by inhalation of the germ into the lungs, and that other ways of infection—cutaneous, intestinal, congenital, etc.—seldom occur. We further believe that infection of the bovine type is negligible in countries where boiled milk is exclusively used. We consider the possibility of one human being infecting another to be so great that we are of the opinion that in most cases of tuberculosis the disease is contracted in this manner.

Behring maintained that tuberculosis in the adult is only the end of a song sung at the cradle of the infant. We now know that this conception must be modified. Tuberculosis of the adult is the end of a song sung during the entire childhood. The first infection usually takes place in childhood, and so the later developments are merely the result of this infection.

We find a primary affection in tuberculosis at the place of entrance of the tubercle bacillus in an alveolus or in a small bronchiolus. There we find a real exudative, inflammatory process in the sense of a pneumonia, caused by the tubercle bacillus. The primary focus is very small—sometimes, even microscopically, hardly visible—and usually no larger than a pea or bean. According to Ghon's statistics, 174 out of 184 cases had a primary affection smaller than a hazel-nut; 83 were as large as a pea, and 24 as large as a bean. Needless to say, we are unable to detect such a small infiltration by percussion

* Cases mostly observed in the Children's Clinic of Vienna, Professor Pirquet. Radiographic pictures taken by Dr. H. Wimberger, Assistant of the Clinic, Vienna.

or auscultation, and even the *x*-ray does not always reveal such a small focus. Only in rare cases when this primary affection grows by spreading to surrounding tissues and so forms large caseous masses or cavities, can we diagnose it, mainly by means of radioscopy. The classical localization of the primary focus is subpleural; more frequently on the right than on the left side, and more often in the upper lobes. Ghon, studying 665 cases with one focus, found the distribution of the primary focus to be as follows:

		Per cent.
Right upper lobe	196	29.0
Left upper lobe	167	25.0
Right lower lobe	126	19.0
Left lower lobe	125	19.0
Right middle lobe	51	8.0
	665	100.0

In his study of the primary focus in 790 cases, Ghon obtained the following figures:

	Cases.	Not found.	Not clear.	Lungs.	Extrapulmonary.	
Vienna	184	2.0	15.0	162.0	5	Small intestine, 3 Right tonsil, 1 Skin, 1
Per cent.		1.1	8.1	88.0	2.7	
Prague	606	1.0	23.0	567.0	15	Small intestine, 11 Nose, 1 Left parotid, 1 Right cheek or intestine, 1 Right tube, 1
Per cent.		0.2	3.8	93.6	2.4	
Summary	790	3.0	38.0	729.0	20	
Per cent.		0.5	4.8	92.0	2.5	

From the primary focus the infection travels along the lymphatic vessels to the regional glands. Anatomically we see some involvment of the bronchopulmonary and bronchial glands on the same side that the primary focus is situated. The glands in the bifurcation become markedly enlarged and diseased. At that moment, when the regional glands in the bifurcation become involved, the first stage of the disease is clinically and

anatomically completed. From the localization of the diseased glands we can infer the situation of the primary focus. The time required to develop symptoms of this first stage, that can be microscopically detected, is about fourteen days. For their clinical manifestation four to six weeks may be needed.

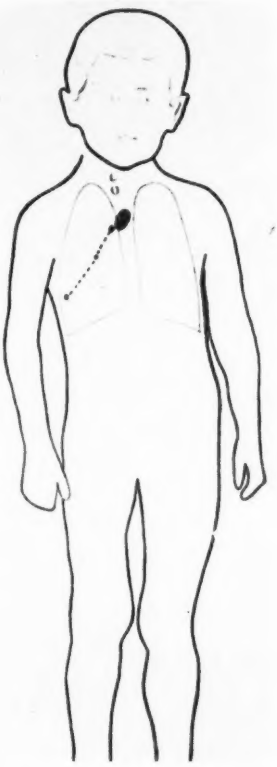

Fig. 96.—Primary focus of infection.

There are reasons for believing that the tubercle bacillus does not stop proceeding at this particular point; it may advance without setting up any other clinical or anatomical signs. The majority of cases of established infection do not show any further

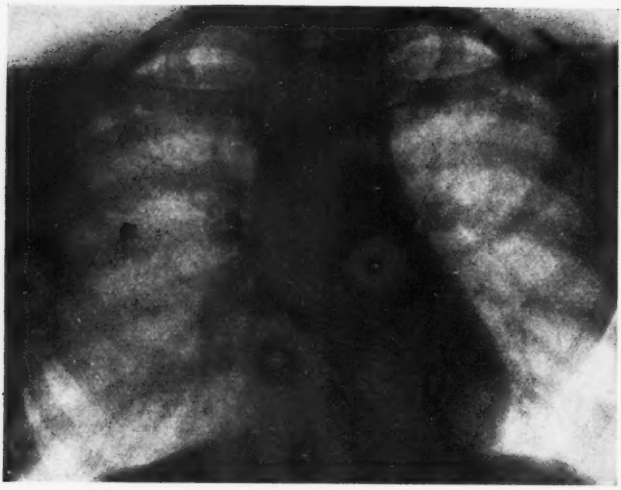

Fig. 97.—Typical picture of a primary focus with calcified regional glands in the hilus.

Fig. 98.—Child six and one-half years, November 11, 1920. About three years after familial infection, showing primary focus with a little calcification just above the right diaphragm and some involvement of the regional glands.

changes, and the visible infection comes to a stop. Because of the fact that the infectious process is arrested for a while at

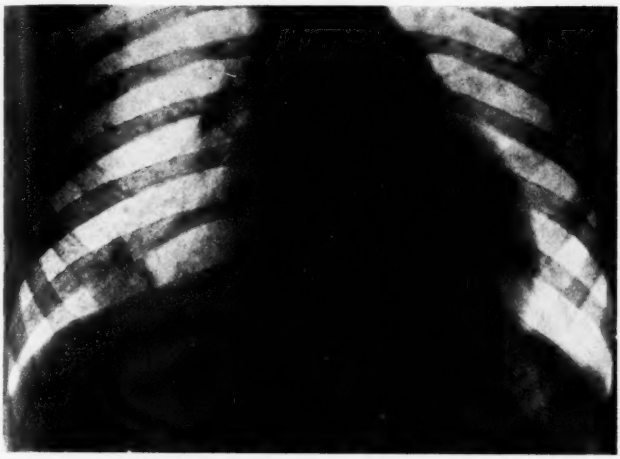

Fig. 99.—Same child as Fig. 98, November, 1922, eight and one-half years of age, calcification more pronounced.

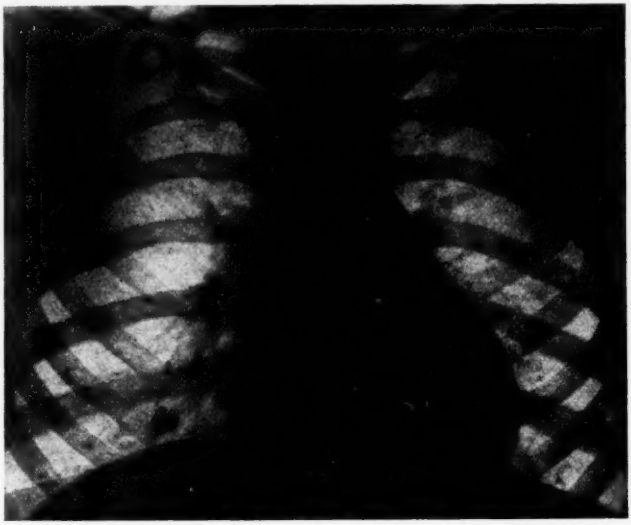

Fig. 100.—Same child as Figs. 98 and 99. Ten and one-half years of age. Calcification of primary focus complete. Shadow much smaller and well defined.

least, we call this well-determined stage of primary focus and diseased regional glands the primary stage, or, according to Ranke, the primary complex.

In cases of mild infection or when the organism is able to resist well, the primary focus heals by scar formation, frequently

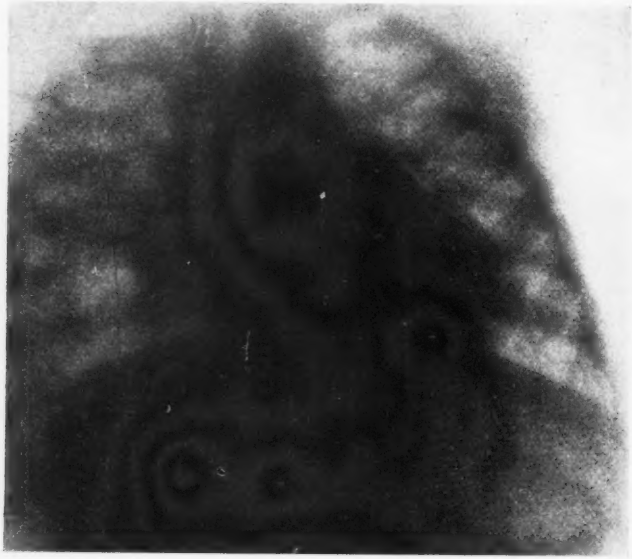

Fig. 101.—Child of eight months, September 17, 1920. Source of infection, tuberculous father. Very extended shadow covering almost the entire right lung field, greater density nearer the hilus and in the region of the right upper lobe. Pirquet test positive; clinical signs of infiltration. This and Figs. 102–104 illustrate development of a primary focus of lung through four years' observation.

with some calcification. The healing process in the infected glands is somewhat slower, the inflammatory process leading to caseinification and later, after many months, to shrinkage and calcification. It is an interesting fact that the primary focus, if it be small, may heal entirely. In the center of the regional glands we still find, even in cases of so-called complete cures, living

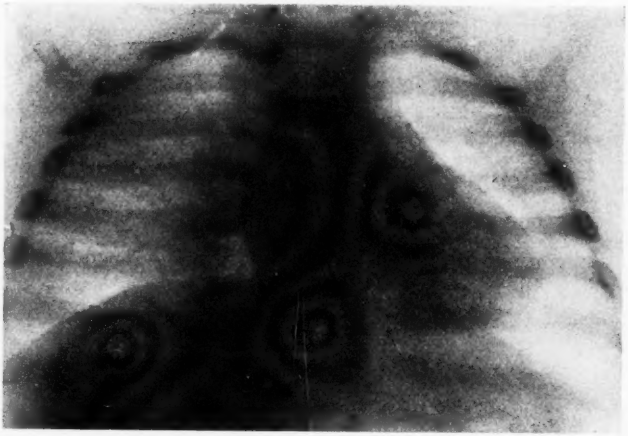

Fig. 102.—Same as Fig. 101. Two months later, showing clearing up of infiltration and demonstrating that it was an epituberculous or pneumonic infiltration and most likely not specific.

Fig. 103.—Same child as in Figs. 101 and 102, now twenty months old. Right lung field has almost entirely cleared up except the hilus region.

tubercle bacilli, the existence and life of which can be proved by their ability to infect guinea-pigs.

The process of perfect clinical healing requires at least two to three years. It is interesting to study these cases roentgenologically. As said before, the primary focus may be radioscopically invisible in its first stage; the enlarged glands only may be seen on the plate. Later, when calcification takes place, the sharp borderline of the primary focus and its distinct,

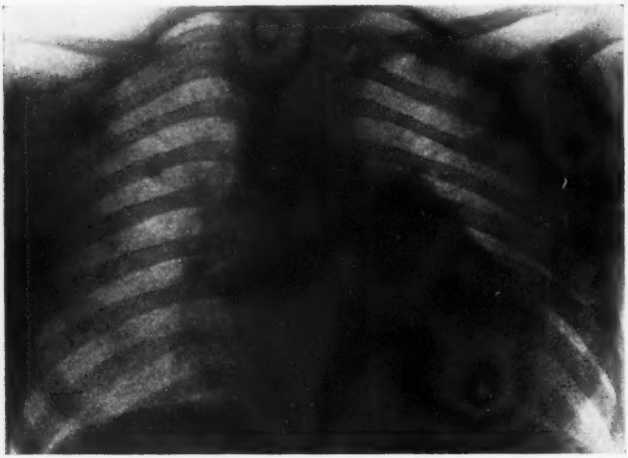

Fig. 104.—Same child as Figs. 101–103, now four years, eight months. Calcified focus is visible and also calcified changes in regional lymph-glands. After four years we are able to see that the primary focus was located in the right upper lobe. The relatively quick clearing up of the infiltrated area speaks for the aspecificity of the shadows in the first picture (Fig. 101).

bone-like shadow make the diagnosis easier. If we find such a definite, projectile-like shadow at a great distance from the hilus, or subpleural, we may make an almost certain diagnosis of a primary focus. Such a picture is the sign of a healing, or of an already healed, primary focus. Similar changes are seen in the glands adjacent to this focus.

These radioscopic findings are important, as calcification in other than tuberculous processes is very rare, and the diagnosis

of a previously established tuberculous infection can thus be made.

The further advance of the tuberculous infection or disease leads to the so-called "secondary stage," which is characterized by the spreading and generalization of the tuberculous virus. There are four ways of dissemination: (1) Lymphatic; (2) hematogenous; (3) bronchogenous; (4) enterogenous.

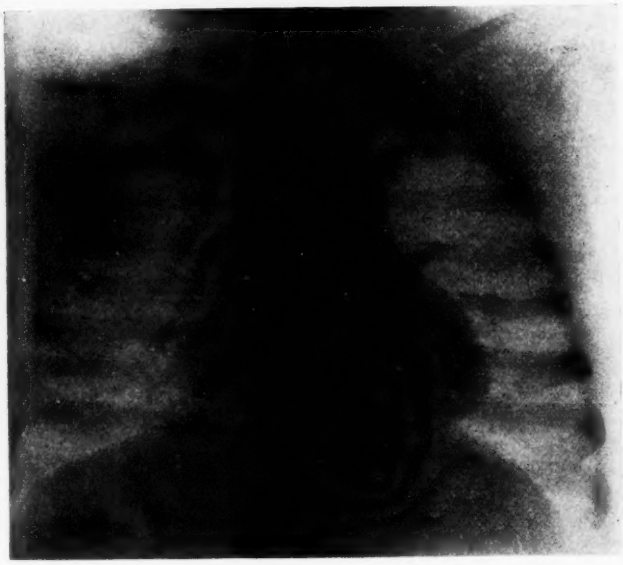

Fig. 105.—Infant of eight months, November 18, 1920. Grandfather of child died of tuberculosis when the child was seven weeks of age. Very soon afterward the child became sickly. Note shadow in hilus and paratracheal. Positive Pirquet test.

The lymphatic route is taken by the bacillus on its way from the primary focus to the bifurcation glands. The infection may now proceed on the same road. We find enlargement of the paratracheal glands, first on the side of the primary focus, later those on the other side become involved, and finally we find diseased glands in the angles of the vena jugularis. Subsequently the tubercle bacillus passes through the ductus thoracicus

Fig. 106.—Same child as Fig. 105, age sixteen months. Increased shadow in the right lung which, after several months, disappeared.

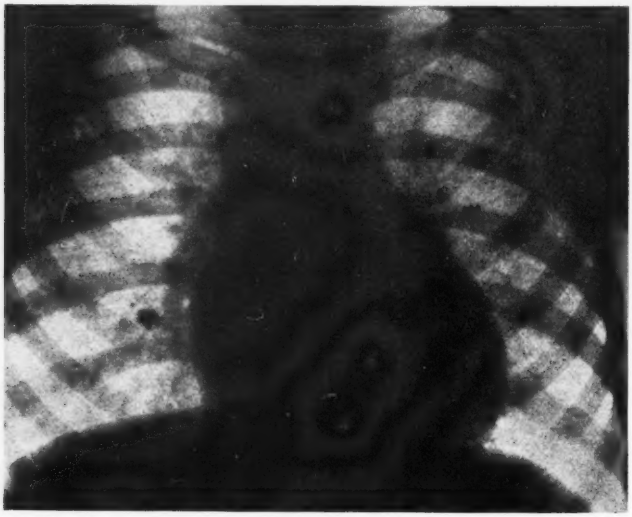

Fig. 107.—Same child as Figs. 105 and 106, three and one-half years of age, showing well-defined calcified focus amid the right lung.

into the vena cava superior and with the blood-stream to the right auricle, right ventricle, arteria pulmonalis, and back to the capillaries in the lungs. This invasion of the pulmonary circulation may produce a miliary tuberculosis in the lungs. The tubercle bacilli can pass the lungs and reach the left part of the heart with the blood-stream and the bacilli are thus set free into the circulation. In this way localization of the tubercle

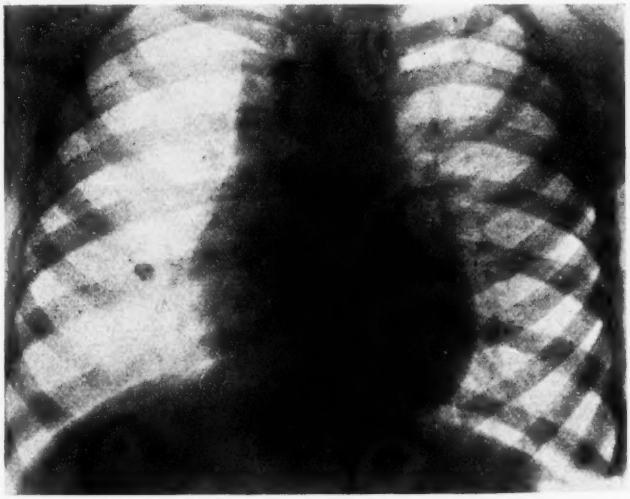

Fig. 108.—Same child as Figs. 105–107. Four and one-half years of age, September 11, 1924. Primary focus well established, calcified paratracheal glands, right side. The characteristic of this case was the relatively quick disappearance of the infiltrative lung process which spoke for the aspecificity of these epituberculous infiltrations.

bacilli in different parts of the body is made possible. The bones, skin, pleura, peritoneum, brain, meninges, etc., may be involved. Any part of the body can be reached. It is easy to comprehend that the final outcome of a tuberculous infection depends on two factors. First, what organ is diseased? We know that miliary tuberculosis of the meninges is almost always fatal, miliary tuberculosis of the lungs very serious, while localization of tuberculosis in the skin or bones permits a much

more favorable prognosis. The second important factor is the quantity of tubercle bacilli set free into the circulating blood. A few tubercle bacilli can be destroyed without being localized. Invasion by a great mass of tubercle bacilli is prone to lead to miliary tuberculosis.

It is a general rule that the younger the child, the more frequent is a massive invasion, with the occurrence of fatal

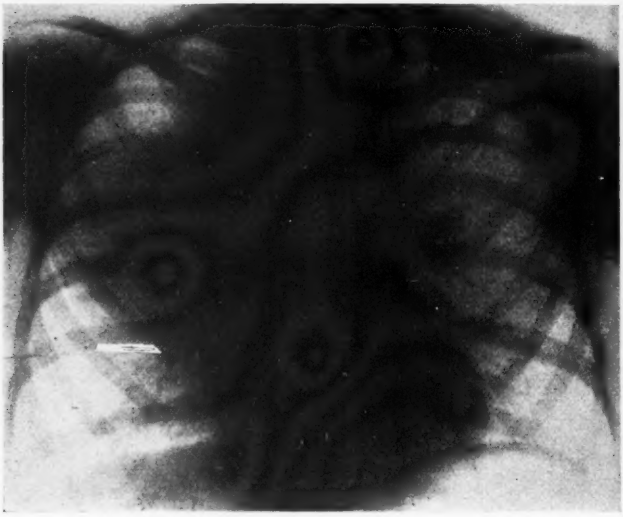

Fig. 109.—Healing of a tuberculous infiltration. Child seven years of age. The source of infection is apparently familial. October 1, 1919, extension shadow reaching almost to the chest wall, right side. Shadow not sharply defined and with greater intensity at the hilus.

forms of miliary tuberculosis of the lungs and other organs, particularly of the meninges. It may further be said that the younger the child, the more quickly does the infection spread from the site of the primary complex into the circulation immediately upon the onset of the infection. The tendency to propagation and to miliary tuberculosis of the lungs and meninges is gradually diminished with increasing age. There is a marked drop in the frequency of tuberculous meningitis in the second

and third years of life. This tendency to propagation and to massive invasion explains the danger of tuberculous infection in infancy. Nearly every infection in infancy leads to a very active disease, and to the imminent peril of tuberculous meningitis and miliary tuberculosis.

Another way in which tuberculosis spreads is the direct invasion of the venous part of the lung capillaries by the bacilli (hematogenous way). Frequently caseated glands adjoining a

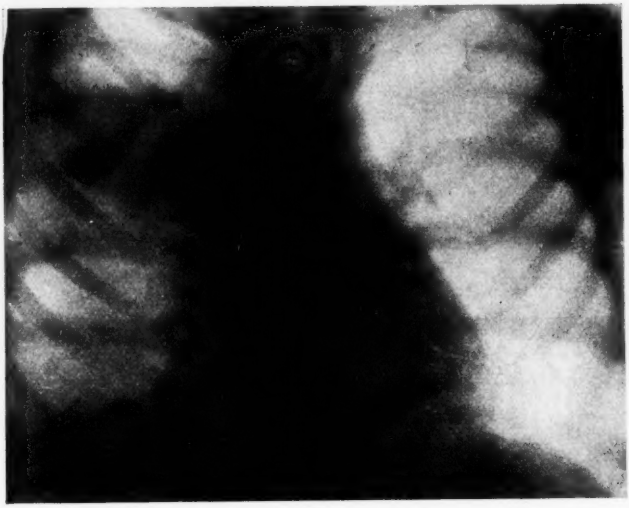

Fig. 110.—Same child as Fig. 107, February 2, 1920. Shadow in right lung field is smaller, more sharply defined, and developing a triangular shape.

pulmonary vein, or located at the angle of the innominate vein, erode and finally break through the wall of the vessels, thus setting the bacilli free in the blood-stream with an effect similar to the one mentioned above, but, nevertheless, differing somewhat. The bacilli, without having to traverse the entire pulmonic circulation, pass directly to the left heart, and the whole mass of the bacilli, without previous filtration in the lung capillaries, reaches the arterial circulation. The inundation of other organs,

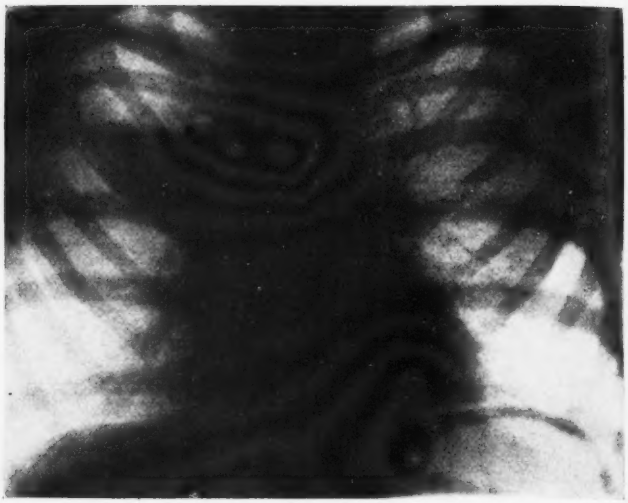

Fig. 111.—Same child as Figs. 109 and 110, October 29, 1920. Eight years of age. Some calcification in the sharply defined triangular shadow. Shadow growing smaller.

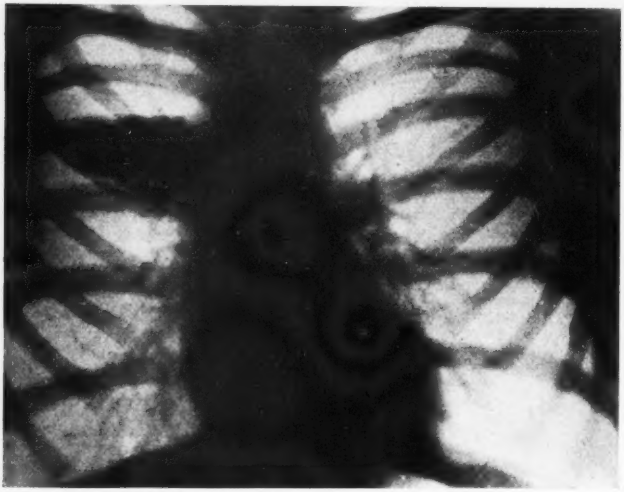

Fig. 112.—Same child as Figs. 109–111, June 7, 1921. Nine and one-half years of age. Calcification more pronounced, honey-comb appearance.

besides the lungs, may, in such cases, be more intensive. We also believe that in this way a massive eruption of tuberculides may be more easily developed in the skin. All organs excepting the lungs are more exposed to infection by the hematogenous way than they are to infection by invasion on the lymphatic route.

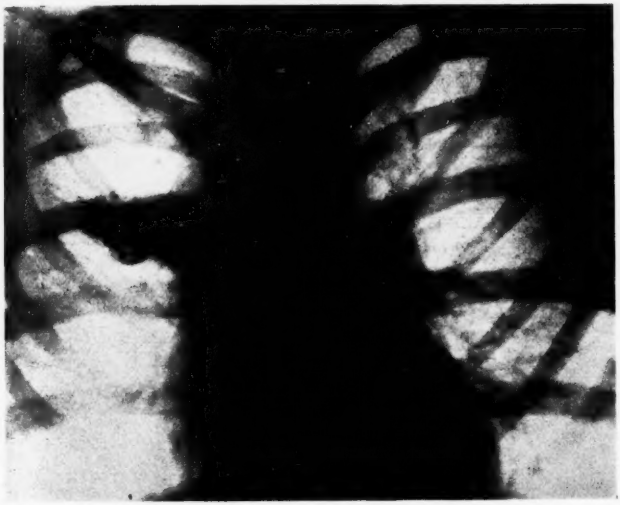

Fig. 113.—Same child, thirteen years of age. Calcified area still present but small, proving that even calcified changes may be absorbed to a certain extent. General condition was poor in the first year of observation, improved gradually and was excellent at the end of observation. Observation shows, furthermore, that even extensive areas of infiltration can be cured.

The third, and a very important mode of spreading tuberculous infection, is by way of the bronchi. Immediately following the first manifestation of tuberculosis in the lungs we see an involvement of the surrounding parts of the lungs. The infectious tuberculous material brought up during expiration and coughing is liable to be aspirated in the next inspiration and conveyed to other parts of the lungs, at first on the same side as the primary focus is situated. By vigorous expectoration the tuberculous

material is brought up to the bifurcation. Now there is a possibility of transmitting this material to different parts of the other lung by inhalation. All these secondary foci can, and frequently do, grow to a mass larger than the primary focus.

Fig. 114.—Secondary stage of infection.

We learn from this that a large tuberculous focus is not likely to be the primary focus, as the latter usually is and remains small.

The fact that the tuberculosis infection takes place in the lungs brings another danger with it. We must breathe, and by

exhalation, inhalation, and coughing, the tuberculous individual spreads the infection within his own lungs. The danger of tuberculous infection depends, to some extent, on the unfortunate circumstance of the first localization of the tuberculosis in the lungs. It appears from many observations that in cases where there is an extrapulmonary entrance of tuberculous bacilli, as, for instance, in so-called circumcision tuberculosis, there is a more favorable prognosis. In these cases the danger of generaliza-

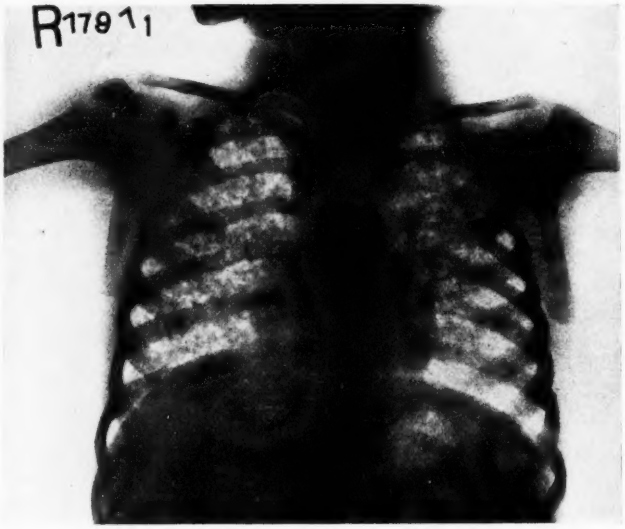

Fig. 115.—Typical picture of miliary tuberculosis in an infant about nine months of age.

tion also exists, and, therefore, of miliary tuberculosis of the lungs and meninges, and there is also some possibility of localization of bacilli in the lungs by the lymphogenous or hematogenous way. But the spreading by the bronchogenous way is less frequent, and is only possible from a secondary focus in the lungs.

With excessive expectoration the tuberculous material is brought higher than the bifurcation, and up to the larynx and nasopharynx. As most young children do not expectorate, but

swallow the sputum, there is imminent danger of conveying tuberculosis to the intestine. This is the enterogenous way of spreading tuberculosis. Thus we find the formation of ulcers, resulting in the involvement of the mesenteric glands. In such cases we find tuberculous bacilli in the stools. Tuberculous ulcers in the intestine indicate not only the disease of the intestine, but also the presence of a destructive pulmonic process in open communication with the respiratory passages, unless the tuberculous process results from a primary localization of the tuberculosis in the intestine.

In the second stage of the disease exudative processes prevail. The younger the child, the less frequent are the proliferating processes. Caseation occurs on account of the poor nutrition of the tuberculous tissue. Cavities may be formed by the destruction of lung tissue, but this is not found as frequently as it is in later life. They have no tendency to chronicity, with the formation of connective tissue. These are acute cavities, due to the rapid destruction of the damaged tissue.

The primary stage in its most marked manifestations lasts several weeks or months. The healing of this process requires from two to three years. The second stage of the disease presents different manifestations. Some cases show only one tuberculous focus; the great majority show more than one localization and several relapses. Each focus individually needs time for development and clearing up. Such repeated tuberculous manifestations can occur all through childhood. Each manifestation may show a tendency toward arrest and restoration, but sooner or later the old focus may flare up again. All the foci in the body usually show the same stage of activity or inactivity, as well as the same progressive tendency to heal. But, on the other hand, we find cases in different stages of tuberculous disease.

Theoretically there is a danger of meningitis tuberculosis and miliary tuberculosis of the lungs at any moment of the secondary stage. Fortunately this tendency to massive invasion diminishes in the growing child. Even the probability of an ensuing secondary stage of tuberculosis is markedly less after

the seventh year. It appears that tuberculous infection in children between seven and twelve years of age is usually arrested in the first stage. Many cases do not show any symptoms of tuberculosis, except a positive Pirquet reaction or a positive intracutaneous tuberculin reaction. We must, therefore, assume that not every infection leads to disease. There is a difference in meaning between the terms "tuberculous infection" and

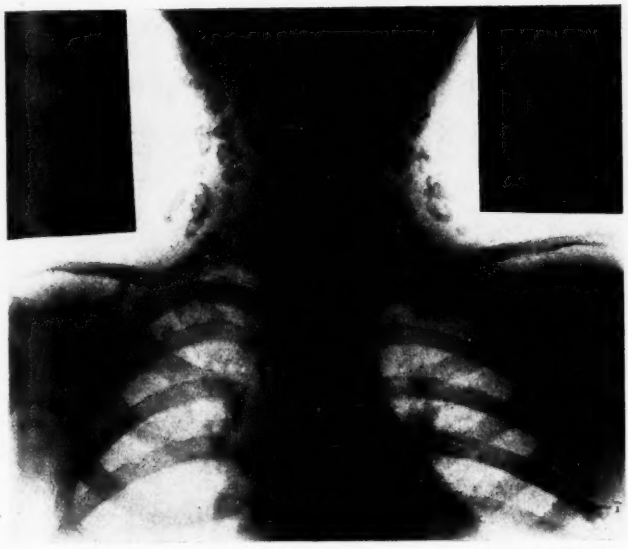

Fig. 116.—Multiple calcified scrofulous glands in neck of child eleven years of age. Stage of calcification combined with active process in the lymph-glands and discharging pus.

"tuberculous disease." If infection takes place, a primary focus is formed with involvement of the regional glands, but this may be so insignificant that even at autopsy there may be great difficulty in finding the primary complex.

In the human organism, which has been subjected to tuberculous infection for many years, the reaction against tuberculosis has become altered. Instead of showing more or less acute, exudative forms of reaction, the organism shows a tendency to

chronic proliferating forms. At this point we say that the disease has reached its third or tertiary stage. The tuberculous process becomes localized in the apical region of the lung. We find the formation of chronic cavities. We do not find the characteristic forms of the third stage before puberty. It is of

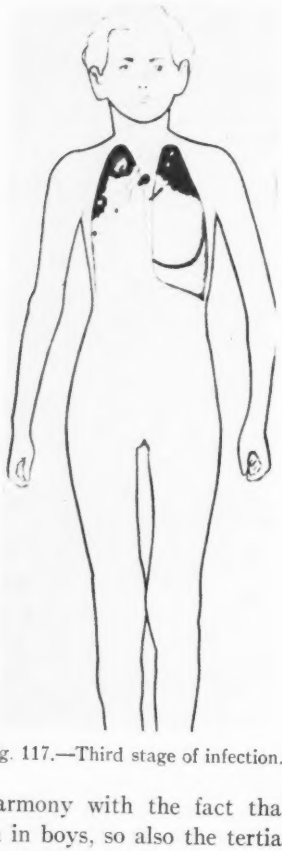

Fig. 117.—Third stage of infection.

interest that in harmony with the fact that puberty occurs earlier in girls than in boys, so also the tertiary form of tuberculosis is seen earlier in girls than in boys, being present in girls about the ninth, and in boys about the eleventh or twelfth year.

A tuberculous infection, occurring in an adult for the first

time, presents symptoms similar to the primary complex in childhood; a primary focus, subpleural or in the lung tissue, and diseased regional glands, with the probability of a consequent second stage. The third stage, however, never immediately succeeds the first and second stages, for even in the adult the organism requires a number of years before reaching the third stage.

These facts obviously prove the theory that the typical forms of chronic tuberculosis in adults cannot occur in individuals previously free from tuberculous infection; the primary stage of tuberculosis must have preceded. A question of paramount importance arises, which is, how does the adult acquire the tertiary stage? Is it the result of a flaring-up of an old infection under influences which lower the resistance against tuberculosis, as, for example, malnutrition, puberty, influenza, etc., or is it the result of reinfection from without?

There is no doubt that repeated reinfection from without may overcome the individual's immunity, which would ordinarily be sufficient protection against less massive and less frequent reinfection from without. But perhaps in the majority of cases the third stage of tuberculosis results from an old tuberculous focus. We must remember that living tubercle bacilli are present in the glands adjacent to the primary focus, even after shrinkage and calcification have taken place. The growing immunity of the organism nullifies the activity of these bacilli, but when the health of the individual is impaired, the tubercle bacillus may break through the wall of its prison and cause active processes. When a tuberculous infection is established, we cannot get rid of the undesirable intruder; we can only compromise, and at best may succeed in temporarily imprisoning it. The tubercle bacillus lives on, however, and may develop dangerous activity. We believe that the high frequency of tuberculosis in certain occupations, as, for instance, nursing, is due to impaired health leading to lowered resistance against an old tuberculous process, and not to a reinfection from without. The importance of the possibility of infection from without cannot, however, be denied, for there is no doubt

that the immunity acquired through the first infection is only relative, and may be overcome by a too virulent reinfection.

It has been pointed out that it is only seldom that we are able to diagnose a primary focus. Extensive areas of dulness, with bronchial breathing, are characteristic of the secondary stage, or of non-specific pneumonic infiltrations (epituberculous infiltrations). In infancy, even during the primary stage, clinical symptoms may be produced by the enlargement of the glands at the place of bifurcation, but in infancy and childhood the diagnosis of tuberculosis is usually made from symptoms of the secondary stage. I call your attention to the cases of bone-joint tuberculosis, scrofula, tuberculous meningitis, and tuberculosis of the serous membranes (pleura, pericardia, peritoneum, etc.).

In discussing the frequency of tuberculosis, we must distinguish between tuberculous infection and the actual disease. About 95 per cent. of all Viennese children under fourteen years of age, admitted to hospital wards or dispensaries, are infected with tuberculosis, but in favorable surroundings only a small percentage of these children show evidence of active tuberculosis. We are convinced that tuberculous infection in itself is not so dangerous, but the future developments depend upon the age of the child at the time of infection, upon the localization of the tuberculous foci, and upon the resistance of the organism. We know that an infant's resistance against tuberculous infection is relatively weak. The majority of such infections lead to disease, and the mortality of infants from tuberculosis is very high during the first few months of life, being about 80 per cent., whereas in the second six months it is about 60 per cent. With advancing years the resistance against tuberculous infection increases, and there are more and more cases which overcome infection without presenting any clinical symptoms. The fight against tuberculosis should, therefore, not only be a fight against the infection itself, but against such conditions as tend to lower the resistance of an individual against the disease. I have no doubt that hygienic housing, fresh air, sunlight, adequate nutrition, and the avoidance of overwork are the real remedies in the fight against tuberculosis.

CLINIC OF DR. BURRILL B. CROHN

MT. SINAI HOSPITAL

POSTTRAUMATIC DIAPHRAGMATIC HERNIA

DIAPHRAGMATIC hernia may be defined as a transdiaphragmatic evisceration of part of the abdominal contents into the thoracic cavity.

From a review of the literature it would appear that such a condition is comparatively rare. Authentic cases, that is, cases confirmed by adequate *x*-ray reports, have occurred in numbers only in the last few years, since the development of radiographic technic. As large an institution as the Mayo Clinic has reported to date only 20 cases of herniation through the diaphragm, at least confirmed by operation. I have seen 3 cases of this condition in my office in the last year, and, although recognizing that such a coincidence may be purely accidental, I am of the opinion that with the rapidly increasing number of automobile accidents, transdiaphragmatic herniation will become a more commonly recognized clinical entity. A brief review of these 3 cases will tend to illustrate most of the important symptoms and physical signs of the condition, and will furnish a basis upon which a discussion of the entire condition may be formulated.

Case I.—A woman, forty-eight years of age, who had been complaining for more than two months of vague abdominal symptoms: epigastric distress, an occasional attack of vomiting, and a loss of 12 pounds in weight. She was a large, well-built woman, rather obese, and inclined to be somewhat neurotic. Because of these symptoms, she was operated upon under the impression that an early carcinoma of the stomach was present, but at the exploratory operation no pathologic condition of any of the viscera was discovered. While convalescing, she began to vomit and to suffer epigastric discomfort and pain. Her vomiting was profuse, copious, never sanguinous, and apparently contained no food residue.

Radiographic examination at this time showed a hernia of the left leaf of the diaphragm, with the stomach almost entirely placed in the left thoracic cavity. The antrum of the stomach was caught in the hernial opening with torsion and constriction of the antral portion. The remainder of the stomach

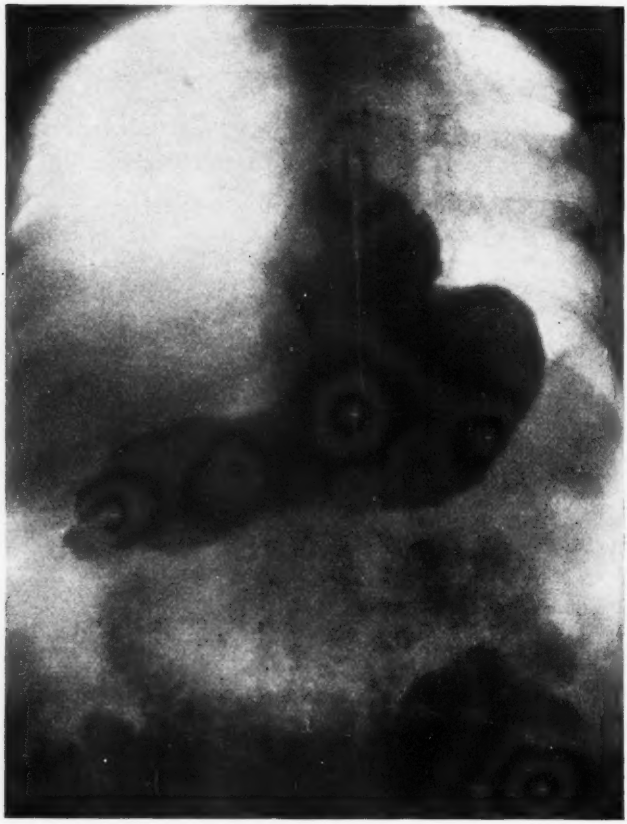

Fig. 118.—Herniation of fundus of stomach through left leaf of diaphragm.

above the diaphragm, was filled with fluid, and was considerably distended. On cross examination, we learned that the patient had fallen on her face violently six or eight months previous to the onset of her symptoms. The trauma was mild in itself, and was yet sufficient to cause the rupture of the leaf of the diaphragm as described.

Following radiographic examination, the stomach was lavaged, but the vomiting continued almost uninterruptedly. Symptoms of tetany now intervened, with mild carpopedal spasm, twitchings of the face, general muscular irritability, and a positive Chvostek sign. Analysis of the blood constituents, in the fasting state, per 100 c.c. showed the following:

Urea, 15 mg.
Incoagulable nitrogen, 49 mg.
Uric acid, 7.7.
Creatinin, 1.8.
Blood-sugar, 140.
Carbon dioxid, 80.5.

One observed a slightly elevated nitrogen figure and a moderate alkalosis. A chlorid estimation of the plasma taken at this point showed 430 mg. to the 100 c.c., a very marked reduction, corresponding with the usual findings in cases of tetany. Persistent gastric lavage, the institution of saline therapy subcutaneously and by rectum, and the administration of calcium chlorid intravenously relieved the tetany, and an operation became feasible.

Operation by Dr. Richard Lewisohn.—A median abdominal incision was made between the ensiform cartilage and the umbilicus. A hiatus in the diaphragm, four fingerbreadths in extent, was found. This opening was stretched. The stomach was delivered back into the abdominal cavity, and the rent in the diaphragm was sutured with several layers of reinforced catgut.

The patient was discharged from the hospital, completely free of symptoms, but, unfortunately, several months later reappeared for examination. She had very mild gastric symptoms, and, on re-examining her radiographically, it was observed that the stomach had again penetrated through the hernia and was once more partly located in the left thoracic cavity. However, she is well at the present time, suffering no symptoms, no loss of weight, and is not conscious of the fact that a recurrence of the abnormal condition has taken place.

Case II.—Male, fifty-two years of age, married, who asserts that four years ago he was operated upon for a supposed ulcer of the stomach, a gastroenterostomy being performed. Following the operation, he was completely well for three years, and was then accidentally hit by the radiator of a large truck which was running at speed. Eight of the ribs on the left side of his thorax were broken, and the pulmonary tissue was pierced. A severe convalescence of nearly two months followed.

The patient apparently regained his full health except for a pain over the left thoracic wall, referred to his back. The pain was actually a feeling of distention which occurred after eating. He was relieved when he restricted his diet. During the week before he presented himself, he had vomited several times, usually at night. His appetite had become poor and nausea occurred after meals. He offered the remark spontaneously that he was much improved after gastric lavage, and had, in fact, induced vomiting to relieve the discomfort of nausea. He had lost no weight and his bowels were regular. There had been no melena and no vomiting of blood, no heart-burn.

The symptoms of which he complained seemed to be entirely dissimilar

to those he suffered before the operation for supposed ulcer. It was apparent, immediately, that he was suffering from one of two conditions: either a recurrent gastrojejunal ulcer at the enterostomy stoma, or a posttraumatic condition involving the upper abdomen and chest. On questioning, it was learned that no ulcer was ever shown in the radiographs before operation, and it seemed very questionable to me that he had ever had an ulcer. Nor did his present symptoms demonstrate the rhythmic periodicity of symptoms one encounters in gastrojejunal ulcer—the severe heart-burn, epigastric cramps, and slow loss of blood characterizing peptic ulceration. The surmise was that, with so severe a trauma, a rupture of the diaphragm had taken place and a diaphragmatic hernia was present.

Proceeding to physical examination, we observed a well-nourished, rather neurotic individual. His pupillary and peripheral reflexes were normal. His tongue was slightly coated and there was a moderately fetid odor to the breath. Thoracic examination revealed the right border of the heart extended to the right mammary line. The left border percussed almost parallel to and slightly to the left of the left parasternal line. The apex of the heart could be palpated very faintly, about the fifth intercostal space, close to the sternum. There was exaggerated resonance over the entire right chest. Over the left apical region, anteriorly and posteriorly, there was dull resonance down to the second space, and an area of tympany on percussion down to the third or fourth space, below which there was complete flatness. On inspection there seemed to be almost complete fixation of the left chest. On auscultation respiratory sounds were normal, or slightly exaggerated over the entire right chest, and completely absent over the left chest except slight audibility over the apical regions. The voice sounds were not carried down over the left chest, except that posteriorly, in the interscapular region, a weak egophony was present. Upon accidentally moving the patient about, a splashing sound was heard over the left chest, easily audible upon succussion. The abdominal examination was negative except for the splashing sound over the entire left hypochondriac and splenic regions.

At first, it seemed likely we were dealing with a left-sided hydropneumothorax with displacement of the heart to the right by a large collection of fluid, yet the history of daily spontaneous vomiting, with symptoms of relief by self-induced vomiting and lavage, made it seem more likely that the free fluid heard in succussion over the entire left side originated in the stomach rather than in the pleura.

On fluoroscopy a level of free fluid was immediately noted about the height of the fourth interspace. The heart was pushed far over to the right chest. Upon administration of the barium meal the confused condition of affairs in the stomach was observed. The cardiac opening appeared at the lowermost portion of the gastric shadow, but more or less at its normal position, opposite the twelfth dorsal vertebra. The pylorus and the prepyloric portion of the stomach as well as the gastro-enterostomy stoma were never definitely seen. But a large shadow of stomach filled with barium below and fluid above, and an enormous magenblasse were seen to occupy almost the entire left chest. Peristalsis was not visible. The duodenum begain to fill soon after the beginning of observations. There was marked delay in gastric

motility. At the six-hour observation and at the twenty-four-hour observation barium was visible in the stomach and duodenum. In fact, the entire duodenum was outlined at both late observations, showing considerable dilatation and puddling. No other abdominal viscera were noted to have passed through the diaphragmatic rupture. The colon was apparently in its normal position, and the spleen and liver did not participate in the herniation. A test-meal showed 240 c.c. removed in the fasting contents; free acidity of 8 and a total acidity of 26, with no sarcinæ or lactic acid present.

The nature of the case was quite evident, and our clinical impression was confirmed by radiographic findings. The position of the stomach was unusual, being entirely within the thoracic cavity. The cardia was the only sphincter visible. The pylorus was not seen, and the gastro-enterostomy stoma was probably at the lowermost portion of the gastric shadow near the defect in the diaphragm. The symptoms were due evidently to retention of food, and to gastric secretion in the viscus. Vomiting was present in this case, as in the first, but not to such a great degree. The general nutrition of the patient had not suffered, and there was no loss of weight. The patient refused to entertain the idea of any operative procedure. He said he was very comfortable, and felt that if he could learn to lavage himself he would regain good health, and was completely opposed to a radical treatment of a condition whose existence came to him as a great surprise. The possibility of a volvulus of the stomach, and even a fair probability that at some moment a complete obstruction of the pylorus or stoma might take place, was presented to him. Besides these possible mechanical complications, we had to bear in mind that the stomach wall, impinging upon a narrow opening surrounded by a strong musculature, is often subjected to superficial ulceration and a bleeding which, although it might be slow, is continuous and may eventually lead to secondary anemia so severe as to resemble the primary pernicious type.

Case III.—Ten months ago, a third case presented herself for treatment. She was a woman sixty-three years of age. She had had slight pains for most of her lifetime. Two years ago she nursed an invalid whom she lifted repeatedly from bed at the cost of great exertion. For three months prior to examination she has complained of epigastric pain radiating around her waist and to the cardiac region, the pains being considerably increased after food and relieved by alkalis and the drinking of milk. She belched and vomited from time to time and has lost 14 pounds in weight.

Physical examination revealed marked dulness over the left lower thoracic cavity, diminished breathing and harsh râles. Roentgen-ray examination showed half of the fundus of the stomach above the diaphragm in the left chest, the fundus being apparently posterior to the heart, and the herniation being apparently through the esophageal hiatus. There was slight delay in gastric motility and a small six-hour residue in the prepyloric region of the stomach. Presumably this was a case of subdiaphragmatic hernia of the acquired type, superimposed upon which were the symptoms of a peptic ulcer, the site of which was probably at the constriction area of the body of the stomach where the firm muscular fibers of the diaphragm impinge upon its wall. Such ulcers are not unusual.

The subsequent history of this case is interesting. A coexisting arterial hypertension, the age and obesity of the women seemed logically to contraindicate surgical manipulation. She was put upon bed rest, restriction in diet and alkalis, and her symptoms entirely disappeared. The relief afforded by the treatment has continued to date, and one may hopefully expect a continuance of this favorable situation.

DISCUSSION

Hernias of the diaphragm, considered from the etiologic standpoint, may be classified as congenital, traumatic, and acquired.

The congenital hernias are due to imperfect fusion of the leaves of the diaphragm, or to imperfect closure of the normal hiatuses in this muscular plane.

Traumatic hernias of the true type result from traumatic stabs or puncture wounds of the chest or abdomen and were most frequently seen during and after the recent war. Rupture of the muscular bundles of the diaphragm may result from any injury or trauma that suddenly creates a greatly increased intra-abdominal pressure, such as are now often seen resulting from automobile or train accidents, or falls from height.

Acquired hernias, practically always traumatic, occur through one of the natural orifices of the diaphragm in the anatomical areas of least resistance. These sites are the esophageal hiatus (the most usual one) and the anterior hiatus, through which the epigastric and internal mammary vessels anastomose. Very frequently the orifice through which the aorta or the vena cava passes may be the seat of such a postnatal herniation. A traumatic hernia may appear immediately after the injury, or may occur some months or years later. It is often difficult to ascertain whether one is dealing with a congenital hernia or to herniation following a mild trauma. With severe trauma the herniation not infrequently passes directly through the muscular planes of the diaphragm regardless of the natural sites of the visceral openings (Cases I and II).

The stomach is the organ most frequently occupying the hernial opening. In the experience of Hedblom, it was prolapsed in 194 out of 378 cases in the literature. The colon

and omentum are frequently associated in this condition; occasionally, also, the spleen or liver. Occasionally small congenital herniations of the fundus of the stomach occur through the esophageal hiatus. These are of little moment, and give no symptoms. In all instances, the hernial sac is practically always on the left side. Right-sided diaphragmatic hernia is rare. The symptoms of diaphragmatic hernia are usually caused by the mechanical effects that result from the pressure of the muscle bundles of the diaphragm incarcerated in the opening. The pressure of the eviscerated organ upon the heart and lungs in the thoracic cavity may secondarily give rise to embarrassment of circulation and respiration.

As has been said, small herniations of the fundus of the stomach through the diaphragm are symptomless, and are usually discovered accidentally in the course of a routine radiographic examination. Slight distress after eating, belching, and some nervousness and anxiety may be present; the general appearance of the patient is more likely to be that of psychoneurosis. The symptoms of true hernia may be periodic, and this may be due, as in our first case, to the fact that the stomach may reduce itself at times and re-enter the abdominal cavity. The original exploratory laparotomy in our first case was done by a very competent surgeon, and yet no abnormal situation of the stomach was observed. Shortly after the operation, however, the symptoms were re-established, presumably due to a recurring herniation of the stomach. This is a very important and interesting fact.

Hematemesis has occasionally been observed to accompany the persistent vomiting in such cases. This may be so marked as to give rise to secondary anemia of a severe nature. The anemia is due presumably to the constant seepage of blood from the pressure effects of the diaphragm upon the incarcerated gastric mucosa. Occult blood is constantly present in the feces of such cases. Strangulation of any part of the herniated viscera may take place with resultant gangrene and death. In diaphragmatic hernia thoracic symptoms may be present. They may consist of a sensation of pressure in the chest, substernal

distress upon swallowing or drinking, dyspnea, and cardiac palpitation. The physical signs may be completely absent in small herniations, or may be evident and as marked as in the second case reported above. One may observe a tympanitic note over the left lower chest posteriorly and laterally, due to the distended fundus of the stomach occupying this area; splashing and gurgling sounds are frequently heard over this area. Marked dulness over the left chest is due to the fluid content of the fundus of the stomach. The eventual diagnosis is made by radiographic examination.

DIAGNOSIS

The only condition from which hernia must be differentiated is eventration of the diaphragm. The diaphragm in eventration may be as high as the level of the clavicle; there may be total congenital absence of one-half of the diaphragm, or the eventrated diaphragm may be so thinned out as to be practically invisible. At times it is difficult to differentiate the two conditions. In eventration one leaf of the diaphragm is definitely elevated, paretic, and moves only slightly, or not at all with respiration. In diaphragmatic hernia the leaves of the diaphragm occupy the normal position and move regularly with respiration.

PROGNOSIS AND OPERATIVE TREATMENT

Instances of small congenital herniation through the diaphragm may occur through adult life without symptoms, and without incapacitating the patient. More often, however, symptoms of incarceration and strangulation are produced by gastric or colonic obstruction, leading eventually, if not relieved, to gangrene and perforation. Operation at such a time is fraught with great risk, and a high mortality.

Operation may be performed either by the abdominal or transthoracic approach. The transpleural or extrapleural thoracic operation is regarded as the method of election, because it gives a greater percentage of permanent cures. The rent in the diaphragm is more easily and durably sutured from above;

the reduction of the hernia is feasible from the pleural side, but difficult from the abdominal approach because of the tremendous suction pull of the negative pressure in the pleural cavity. Inaccessible hernial openings, particularly at the esophageal ring, may by necessity be impossible of permanent repair; or the closure of a large defect in the diaphragm may be either impossible or unsatisfactory. In such instances, the stomach may be sutured to the anterior abdominal wall to prevent the recurrence of its herniation.

RESULTS

The operative mortality in diaphragmatic hernia, as culled by Carman and Fineman, from a collected series, was 33.6 per cent. In the non-obstructive cases, the mortality was 23. 4 per cent. The existence of obstruction practically doubled the death-rate. The operative mortality in the transthoracic type of approach is considerably lower (19.8 per cent.) than following laparotomy (42.9 per cent.).

Recurrence of the hernia following operation is not unusual.

CLINIC OF DR. A. S. BLUMGARTEN

LENOX HILL HOSPITAL

UNUSUAL FORMS OF HYPOTHYROIDISM

1. **Mild Myxedema in Two Sisters.**
2. **Severe Menorrhagia Due to Hypothyroidism.**
3. **Severe Metrorrhagia Due to Hypothyroidism.**
4. **Mild Myxedema in a Patient with Constitutional Autonomic Dysfunction.**
5. **End-result of Cretinism after Sixteen Years of Continued Thyroid Treatment.**

THE diagnosis of hypothyroidism has been greatly simplified by the introduction of basal metabolism tests into clinical medicine. As a rule, however, a basal metabolism test is not done unless there is sufficient clinical evidence to warrant it. The typical cases of adult or infantile myxedema are readily recognized, but in atypical cases the cardinal symptoms of the disease remain in the background and the clinical picture is dominated by unusual symptoms which do not suggest the underlying condition. I wish, therefore, to present several cases of adult hypothyroidism with atypical symptomatology. In some of the cases the cardinal symptoms were so slight that the disease was not even suggested, while one of the cases presented an unusual combination of hypothyroidism with symptoms generally associated with hyperthyroidism. A positive diagnosis was made in all the cases by several careful basal metabolic tests done by the gas analysis method with the Baily modification of the Tissot-Haldane apparatus and checked by the disappearance of the symptoms after intensive administration of thyroid extract.

Typical hypothyroidism occurs in two forms: Adult hypothyroidism or myxedema and infantile myxedema or cretinism. The symptomatology is the same in both with the exception that disturbances in growth and mental development occur in the infantile form in addition to the cardinal symptoms of the adult form.

SYMPTOMATOLOGY OF MYXEDEMA

Hypothyroidism directly or indirectly affects nearly every organ of the body and we may, therefore, divide the symptoms into several groups as follows:

1. Skin symptoms.
2. Metabolic disturbances.
3. Cardiovascular symptoms.
4. Blood changes.
5. Gastro-intestinal disturbances.
6. Psychial symptoms.
7. Disturbances in the nervous system.
8. Genital and urinary symptoms.
9. Disturbances in the teeth.

The skin symptoms are the cardinal symptoms of myxedema. The skin is dry, pale, yellowish, and has a peculiar soft edematous feel, yet it does not pit, and is often pigmented. In a typical case the entire skin and the mucous membranes are involved. The face is puffy, the eyelids are swollen, the palpebral fissures are narrow and the expression is dull and stupid. The nose and lips are thickened, the tongue is often swollen, and the mucous membranes are dry and swollen. There are peculiar edematous pads in the supraclavicular spaces, and the chest and abdomen have the characteristic edematous feel. The electrical conductivity of the skin is markedly diminished. The hair becomes dry and thin and falls out readily. In mild cases the typical appearance of the skin occurs only in the ankles, the legs and face, and the hair on the outer part of the eyebrows falls out. The hands and feet are cold and the nails develop longitudinal ridges and become brittle.

The disturbances in metabolism are usually quite marked. The basal metabolic rate is reduced in proportion to the severity

of the disease and this is the diagnostic feature of the disease. This is due to lessened oxidation. Nitrogen and water are retained and the weight is increased. Carbohydrate tolerance is increased and the specific dynamic action of protein is normal.

The cardiovascular symptoms are typical. The heart action is usually slow and Zondek has demonstrated a myxedematous heart—a temporary dilatation demonstrable by *x*-ray, which subsides under thyroid therapy. Typical electrocardiographic changes have been demonstrated, but these are probably due to diminished conduction of the skin, which prevents proper conduction by the electrodes. The blood-pressure is usually within normal limits, but the vascular tone is diminished as is indicated by lessened vasomotor response. Several observers have demonstrated atheromatous changes in the blood-vessels.

The blood changes are not constant. A severe secondary anemia is usually present in most cases of myxedema, at times, with poikilocytosis and nucleated red cells. As a rule, the leukocytes are normal or reduced, the lymphocytes, monocytes, and eosinophils are increased. The blood-viscosity is increased, the blood-sugar is normal, and the cholesterol content of the blood is increased.

The gastro-intestinal symptoms are not typical, the secretory changes in the stomach are variable, but atonic constipation and a tendency to tympanites are more or less constant symptoms.

The outstanding psychical manifestation is general mental sluggishness, thought is slow, memory is poor, and there is a lack of initiative. In severe cases melancholia and even definite hallucinations or psychoses develop.

Some cases of myxedema complain of severe pressure sensations on top of the head, especially at night. Rheumatic pains in the joints, especially in the spine, have been described by Hertoghe.

In females the genital symptoms are often the outstanding symptoms of the disease. Severe metrorrhagia is the most common symptom and responds readily to thyroid therapy. Chronic cases of myxedema often develop amenorrhea. However, the hypothyroid woman may conceive and give birth to

normal children. Impotence occasionally develops in male patients.

The urine in myxedema often shows occasional casts and a trace of albumin, and edematous swelling of the bladder and urethra has been described.

The changes in the teeth of myxedematous patients are not typical. When they occur they consist of extensive caries and premature falling out of teeth.

Although a careful examination of the myxedematous patient will reveal changes in the various systems of the body, the outstanding symptoms are the skin changes, the circulatory symptoms, and the typical mental sluggishness. When, however, the disturbances in other systems dominate the clinical picture the hypothyroid etiology becomes obscure. The most common chief complaints in most of the atypical forms of myxedema are the following:

1. Rheumatoid pains.
2. Severe menorrhagia, or metrorrhagia.
3. Anemia.
4. Obesity.
5. Pressure on top of the head.
6. Severe atonic constipation.

The following cases illustrate some of these atypical forms of hypothyroidism.

CHRONIC HYPOTHYROIDISM IN TWO SISTERS

Case I.—A. P. A young single woman of twenty-seven came under observation for swelling of the ankles and legs.

As long as she can remember her ankles and legs have been swollen. The swelling has frequently extended up as far as the thigh. Her weight remains stationary but she gains in weight occasionally. At times she gets shortness of breath. She has had low blood-pressure for some time, and she does not perspire readily. She is very fond of sweets. She is a school-teacher by occupation and has always gotten along well in her studies and has had no difficulty in her work.

She has never had any previous illnesses

Menstruation began at thirteen or fourteen, it is always regular, and lasts four days. It is usually painful at the beginning.

The family history is negative.

Physical examination showed a rather tall, well-developed blonde young woman, weighing 154½ pounds, and 168.8 cm. in height. Pulse is 68. Blood-pressure, 125/80. There were no abnormalities of the skull, the throat was congested, and the tonsils were rather small and infected. The thyroid could not be distinctly felt. There were no abnormalities of the lungs or heart, and the abdominal viscera were all normal. The most striking positive finding was a peculiar edematous condition involving the ankles and legs, and a rather dry skin. The basal metabolic rate was *minus 19 per cent.*

The urine examination showed a specific gravity of 1.020, it contained no albumin, sugar, casts, or other abnormal constituents.

Comment.—This patient was evidently suffering from a definite thyroid deficiency. She was given increasing doses of thyroid extract and in the course of about six weeks the swelling of the extremities subsided and her basal metabolic rate was raised to minus 11 per cent.

Case II.—E. P. A young woman of twenty, a sister of the previous patient, came for observation in March, 1927, complaining chiefly of a slow but steady gain in weight, the obesity being confined principally to the lower half of the body. She has no headaches and practically no other symptoms. She had joined a hospital training school and had to give up her nursing course because she couldn't keep up with her studies.

Her past history was practically negative.

Menstruation began at fourteen, it was always regular, profuse, and lasts about a week. It is not accompanied by any symptoms.

Her family history was practically negative except that her older sister is under treatment for hypothyroidism.

Physical examination revealed a rather tall, broad statured young woman weighing 167½ pounds, and 172 cm. in height. The pulse is 86 and the blood-pressure 100/60. The skin was rather dry and scaly, the hair was dry and absent on the outer part of the eyebrows. The eyelids were puffy and the palpebral fissures were narrow. The teeth were in good condition. The thyroid could not be definitely felt. The chest was well developed and no abnormalities of the lungs and heart were present. The abdominal viscera were all normal. The extremities were normal. The basal metabolic rate was *minus 17 per cent.* The urine examination showed a specific gravity of 1.022, it contained no albumin, sugar, or casts.

Comment.—This patient was evidently suffering from a definite thyroid deficiency, which accounted for her obesity and mental sluggishness. She was placed on thyroid extract and in the course of about six weeks the swelling of the extremities subsided, she lost 5 pounds in weight, her mentality improved and her basal metabolic rate was raised to minus 7 per cent.

SEVERE MENORRHAGIA DUE TO HYPOTHYROIDISM

Case III.—D. L. A young girl of eighteen was referred for examination because of a severe secondary anemia resulting from a very severe menorrhagia. She was perfectly well until Labor Day, 1925 when following an automobile accident she began to menstruate and she kept on bleeding pro-

fusely with only very slight remissions until February, 1926. After administration of ergot and similar remedies the bleeding stopped for a while but it soon recurred and the loss of blood was so severe that two transfusions were necessary. Her red cells at that time went down to 2,580,000 and the hemoglobin to 50 per cent. She responded to the transfusions, the bleeding stopped for a few months but it recurred for a day. The following month, however, menstruation occurred, but more profuse than before and each subsequent month the quantity increased. At the onset of the illness she also had an attack of colitis.

She had scarlet fever and chickenpox in childhood.

She began to menstruate at seventeen, she menstruated only once and it lasted four or five days. This was followed by amenorrhea for a year and then the type of menstruation was as indicated in the present history.

Her family history was practically negative.

Physical examination showed a rather thin girl weighing 86 pounds, and 152.5 cm. in height. Her mental processes were sluggish. The skin was very dry, scaly, and puffy. The hair was dry, thin, and silky, the axillary hair was very sparse and the hair on the eyebrows was thin, and there was a slight diminution of pubic hair. The palpebral fissures were narrow and the upper lids were puffy. The tonsils had been removed. There was no distinctly palpable thyroid. The breasts were well developed and the lungs and heart were normal. The abdominal viscera were normal except for a tendency to gastroptosis and intestinal distention. The upper extremities were rather thin. The ankles were rather puffy. Rectal examination showed no abnormalities of the genital organs. The blood examination showed:

Red blood-cells	3,586,000
Hemoglobin	70 per cent.
Leukocytes	8800
Polynuclears	57 per cent.
Small lymphocytes	36 per cent.
Large lymphocytes	4 per cent.
Eosinophils	3 per cent.

The urine examination showed specific gravity 1.018, no albumin, sugar, casts or other abnormalities.

Comment.—There was no evidence of organic disease on physical examination but the rather sluggish mentality, the late onset of menstruation, the dry and puffy skin suggested a possibility of a thyroid deficiency as an underlying cause of the menorrhagia. Consequently two basal metabolic tests were done at intervals of a week, and the tests showed *minus 35 per cent* and *minus 34 per cent.* We were therefore dealing with a patient who had a chronic hypothyroidism in which the menorrhagia was the outstanding symptom and dominated the clinical picture.

The patient was put on large and increasing doses of thyroid extract, the profuse menstrual bleeding gradually subsided, and in two months her red blood-cells increased to 4,480,000, the hemoglobin to 85 per cent. and the basal metabolic rate to minus 8 per cent.

A CASE OF METRORRHAGIA DUE TO HYPOTHYROIDISM

Case IV.—E. S. A young girl of fourteen was referred for examination because of metrorrhagia.

The patient began to menstruate at the age of eleven, the menstruation was regular until twelve, lasting five or six days, and in normal quantities. Since the age of twelve, however, she has bled profusely at each menstrual period and also between periods. At the present time she menstruates every two weeks for five or six days, the menstruation is very profuse; it is not painful except occasionally when she has some slight pain on the fourth day. She has steadily gained in weight and now weighs 120 pounds. She sleeps well, she goes to school and does quite well in her studies. She never feels drowsy and she has no palpitation of the heart. Her secondary sex characteristics have developed normally.

She has had mumps, measles, and grippe.

The family history is negative. Her father is forty-two, rather broad statured. The mother has had a disturbance in hearing for fifteen years. The mother has had several miscarriages and one stillbirth.

Physical examination showed a rather broad-statured, exceptionally well-developed, short young girl weighing 125 pounds, and 158.2 cm. in height; the pulse was 74, and blood-pressure 105/70. The skin was rather dry, the scalp was covered with very fine, silky dry hair. There was considerable growth of hair on the extremities. The palpebral fissures were very narrow and the upper lids were very puffy. The teeth were in excellent condition, of normal development, the tonsils were absent, having been removed. The thyroid was not palpable. The breasts were unusually well developed for her age. The thoracic viscera were normal and the abdomen showed no abnormalities of any of the intra-abdominal organs. The upper extremities showed slight puffiness at the wrists and hands and the lower extremities showed a marked adiposity of the legs, thighs, and puffiness of the ankles. The secondary sex characteristics were unusually well developed for her age. A gynecologic examination had been done and no organic disease of the uterus and adnexa was found on rectal examination. The blood examination showed:

Red blood-cells	4,200,000
Hemoglobin	85 per cent.
White blood-cells	10,000
Polynuclears	68 per cent.
Lymphocytes	30 per cent.
Eosinophils	2 per cent.

Examination of the urine showed no abnormal findings. The basal metabolic rate was *minus 25 per cent.*

Comment.—In view of the fact that we had definite evidence, according to the basal metabolic rate, of hypothyroidism, the patient was put on intensive and increasing doses of thyroid extract. Her metrorrhagia and menorrhagia subsided promptly and at the present time the patient has led a normal menstrual life and is in excellent condition.

A CASE OF MILD MYXEDEMA IN A PATIENT WITH CONSTITUTIONAL AUTONOMIC DYSFUNCTION

Case V.—C. S. A widow of forty-four came under observation for severe headaches of four months' duration. The headaches were constant and the patient described them as a "severe pressure on the top of the head." The illness began five months previous, following the death of her husband, who had been quite ill for ten years and whom she nursed during the entire time. She has always been quite nervous, a condition which was exaggerated by the illness of her husband. She went to her physician, who, because of her nervous symptoms and the fact that the thyroid was somewhat enlarged, said that she had hyperthyroidism, but a basal metabolic test was not done. At times she would have attacks of gastric symptoms with pain. During these nervous attacks she belches a good deal, and she has fine tremors of the hands and palpitation of the heart. She perspires profusely and gets hot flushes at times. Her eyes were examined and presbyopia was found.

Menstruation began at thirteen, it was always regular, and lasted two or three days, but she always felt nervous and exhausted at that time. She gave birth to one son who is now twenty-two years of age. For the last few months her menstruation has stopped.

The family history is negative except that one older sister has diabetes and there is a tendency to obesity in the family.

Physical examination showed a tall, dark complexioned, rather apprehensive, middle-aged woman weighing 168½ pounds, and 167.2 cm. in height. The pulse was 106, and the blood-pressure 135/85. The skin was dry, pale, pigmented, and puffy, and had a typical myxedematous appearance. The scalp was covered with dry, rather fine, silky hair tinged with gray, which had a tendency to fall out. The eyebrows were rather thin. Both upper and lower lids were rather puffy. The teeth were in excellent condition and well developed. The neck showed a palpable thyroid which was apparently slightly enlarged. There were supraclavicular fat pads, abdominal adiposity and marked adiposity around the trochanteric region, thighs, and the legs.

x-Ray examinations of the skull and sinuses were taken, all of which were negative. The urine examination showed no abnormal findings.

The possibility of hyperthyroidism was suggested by the pulse-rate and the nervous symptoms, but the appearance of the skin suggested myxedema. A basal metabolic test was therefore done and the result was *minus 18 per cent.* Accordingly the patient was put on increasing doses of thyroid extract with prompt relief of her symptoms.

Comment.—The clinical history and some of the objective findings indicated that the patient was evidently suffering for years with a constitutional autonomic dysfunction, indicated by her attacks of perspiration and palpitation, tremors, and functional gastric symptoms. As a rule, when these symptoms become intensified or develop at the menopause, they are not due to hyperthyroidism because repeated basal metabolic tests on numerous patients indicate that the basal metabolic rate at the time of the menopause and because of the menopause does not usually increase. The usual

menopause symptoms are due to disturbance in the function of the autonomic nervous system rather than to hyperthyroidism. In this case, however, on top of long-standing symptoms of autonomic dysfunction the patient developed hypothyroidism or a slight myxedema. Consequently the symptoms for which she came under observation were due to the hypothyroidism because there was evidence of a low basal metabolic rate and her symptoms responded to thyroid therapy. The presence of a tachycardia and nervous symptoms as the result of a long-standing constitutional condition were misleading and led to a supposed diagnosis of hyperthyroidism and consequently thyroid therapy, which was the indicated therapy, was not administered.

A CASE OF CRETINISM AFTER SIXTEEN YEARS OF THYROID TREATMENT

Case VI.—M. M. A young, single school-teacher came under observation for "thyroid trouble."

In 1912 her mother noted she was stunted, did not grow, developed fat pads, and was mentally sluggish. She was taken to the family physician, who recognized the condition as cretinism. He put her on 1 grain of thyroid a day and with slight increase in the dosage at times, she has kept up this treatment ever since. As a result she grew 4 or 5 inches within several years, the fat pads disappeared and her mentality improved. For a time while she was away to boarding school she stopped taking the thyroid and the fat pads promptly returned and her mentality became sluggish again. She got along well in school, entered normal school, graduated and is now teaching school. At the present time her only complaint is drowsiness at times, a dry skin, and failure to perspire readily. Her weight has not increased. In October, 1921 she applied for a position which necessitated a physical examination. The doctor told her she had heart trouble. She stopped the thyroid and all her symptoms returned. About four or five years ago her family physician died and she kept on taking the thyroid without medical supervision. About a month ago she went to his successor who had a basal metabolism test done with a small portable apparatus, which showed *minus 38 per cent.* She was then advised to increase the thyroid dosage until she was taking 15 grains a day.

She had chorea when she was three and a half years old, with three recurrences, and an attack of rheumatic fever complicated by endocarditis.

Menstruation began at fourteen, it was always irregular, occurring every five or six weeks. At that time she feels a lack of "pep." She is not emotional and is not much attracted to the opposite sex.

She has always lived in a non-goitrous region, her father died of cancer, her mother is alive and well, and her family history is otherwise negative.

Physical examination showed a rather short, dark complexioned young girl, weighing 111 pounds and 155.5 cm. in height, who looked like a girl of thirteen or fourteen. The pulse was 82, and the blood-pressure 110/70. The patient had a slight cretinoid appearance of the face. The secondary sex characteristics were normal. The skin was soft, dry, and rather scaly. The scalp was covered with dry, curly brown hair and there was no axillary hair,

but pubic hair was present. The palpebral fissures were narrow, the lids were slightly thickened and the pupillary reactions were normal. The teeth were short, well developed, and had no caries. The tonsils were absent, having been removed. The thyroid was palpable but rather small. The heart was not enlarged, the sounds were regular, of good force and quality and there were no murmurs heard. The lungs were normal on physical examination. The upper extremities were rather thin and the hands narrow, of infantile appearance, cold, dry, and cyanotic. The lower extremities were normal.

The urine examination showed no abnormal constituents. The basal metabolic rate was *minus 12 per cent.* by the gasometer method (the patient was on thyroid therapy for several months before the test).

Comment.—The interesting feature in this case is the end-result of sixteen years of thyroid treatment of cretinism, and the small doses of thyroid extract with which normal function could be maintained. As long as the patient was kept on thyroid extract her mentality was accelerated to such an extent that she could go through school, normal school, and was even able to teach school on graduation, but as soon as she stopped the thyroid the symptoms of hypothyroidism promptly returned.

CLINIC OF DR. HENRY JAMES SPENCER

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CLINICAL OBSERVATIONS CONCERNING THE OBESE

OPINIONS regarding the problems of obesity and overweight are so varied and, in some cases, so diametrically opposed, that one is at a loss for a safe basis of judgment when dealing with fat persons. This was the situation when I undertook the treatment of obesity in a separate department of the Clinic of the Cornell University Medical College four years ago and began to collect information to be used as a basis for more rational treatment.

Data were gathered covering the family and personal histories of the patients on points bearing directly upon body weight, such as "heredity," feeding habits, physical activity, and the like. Two hundred and fifty-two obese or overweight persons furnished the sources of information. For working purposes only tentative assumptions were made as the basis for the gathering of data. The answers to these assumptions, for the most part, could be definitely positive or negative. Questions were framed so as to eliminate the personal factor as far as possible. When characteristics of relatives well known to the patient were sought, definite weight and height figures were secured whenever possible, for opinions of individuals as to what constitutes thinness, average height, or fatness, vary greatly. Similar consideration of other factors concerned will demonstrate faulty or more precise and acceptable methods of history taking. As a further example, we never asked whether a patient at that time ate lightly or heavily, but we always asked for a statement of a sample day's diet, and, using the method of measurement by volume set forth by Huddleson in her book, "Food for the Diabetic," we calculated roughly the food intake of carbohydrate, protein, and fat.

TABLE I

Sex and Civil State of 252 Obese Patients

			Per cent.
Females:	Married	163	64.7
	Widowed	26	10.3
	Separated	6	2.4
		195	77.4
	Single	40	15.9
	Total	235	93.3
Males:	Married	12	4.8
	Single	5	1.9
	Total	17	6.7
Grand total		252	100.0

Table I shows a great preponderance of female patients—235 females to 17 males. These figures must not be taken to indicate the sex distribution of overweight. When we analyze the numbers of brothers and sisters who are described as obese and add the patients themselves in the families used we get the following figures: 186 families contained 770 sibs, or 325 males and 445 females (42 per cent. and 58 per cent., respectively), of whom 174 males and 334 females were obese (53.5 per cent. of males and 75 per cent. of females were obese). Thus obese males formed 22.6 per cent. and obese females 43.4 per cent. of the 770 sibs and 34.3 per cent. and 65.7 per cent., respectively, of the 508 obese sibs.

It is not entirely clear why so many more women applied for treatment. The reasons that immediately occur to one's mind do not seem to be the fundamental ones. Thus the preponderance of married women as against those single, widowed, and separated, speaks somewhat against vanity or the desire to be attractive as a cause. The causes of application for treatment will be discussed later.

The times in life when obesity sets in were investigated, but the material is not readily arranged in tabular form. For women, the importance of certain periods of life is clearly evident. These critical periods are (1) about the time of, or shortly

after, marriage; (2) the time of recurring pregnancy; (3) the time when children leave the home for school; (4) the menopause.

When a woman has settled upon and secured her mate she often starts her gain in weight. On her part is the sense that she has attained her goal and can rest back at ease. The candy, the nearby larder, the teas, the ice cream, or other refreshments in which she indulges with her women friends after the moving picture show, are also important factors. Moreover, the activity of office or shop in the premarital career or of dancing or hiking in the period of courtship, is gone. Her husband's desire abundantly to supply her wishes and to support her in leisure works in the same direction. In such ways increased food intake and reduced physical activity come to play their parts.

When pregnancy ensues, doctor and family, custom and physical state conspire to keep her inactive and overfed. When the children reach school age and leave her free for a few hours of quiet she settles back with a sigh of relief. When menopause occurs she again meets conditions which tend to render her inactive. And it is characteristic of many persons that although physical activity is reduced, the food intake is not. "Appetite" is a combination of habit and hunger.

Regarding the person "fat since born," we will refer here only to exogenous factors. I am leaving out practically all consideration of endogenous factors as too involved for this brief discussion. The influence of the thyroid and pituitary glands is well known. Analysis of the data covering the environment of the home as regards kind and quantity of food taken shows rich food and large intake, as a result of family example or urge, as prominent factors. Bound up with this is the example of slow, economical physical movements set by the family, at least its obese members. Careful observation will, I believe, convince any unbiased person of the economy of physical effort practised by the obese. But this is a factor difficult to analyze with scientific satisfaction. Table II, on the occurrence of obesity among close relatives, is interesting in this connection. The percentages are of the total instances in each case where seemingly accurate data could be secured. Figures regarding

TABLE II

Occurrence of Obesity Among Immediate Relatives

	Per cent.		
Maternal:			
Grandfather,	31.6	Grandfather and Grandmother, 24.8 per cent.	All Grandfathers and Grandmothers, Paternal and Maternal, 11.9 per cent.
Grandmother,	34.8		
Uncles	29.3		
Aunts	33.1		
Paternal:			
Grandfather,	18.8	Grandfather and Grandmother, 18.8 per cent.	
Grandmother,	25.6		
Uncles,	20.0		
Aunts,	25.5		
Father,	50.8	Father and Mother, 33.4 per cent.	
Mother,	55.0		
Brothers,	40.5		
Sisters,	47.9		

the maternal grandparents, for example, were not used where facts about only one could be secured. It is interesting to note the higher incidence of obesity among the females and among the maternal predecessors. The same trend was seen in the figures on sibs. Larger statistics might easily overthrow these percentages. That obesity is inherited, in the exact sense of the word, may be doubted.

Many patients dated the beginning of their obesity from convalescence after an operation or a confining illness. The physician and surgeon should learn to guard against overfeeding to promote convalescence. The results do not always warrant the means or the aim.

The age at which the 252 individuals applied for treatment is of small importance, for this was, in most instances, the time when disturbing symptoms appeared. However, when the time of puberty is taken roughly as the beginning of the first important decade, the figures divide themselves as follows: Five to fourteen years, 5 individuals; fifteen to twenty-four years, 19; twenty-five to thirty-four years, 59; thirty-five to forty-four years, 73; forty-five to fifty-four years, 57; fifty-five to sixty-four years, 33; and sixty-five to seventy-four years, 6. The rapid rise after twenty-four years is due to the appearance of uncomfortable symptoms caused by obesity, the rapid drop after sixty is due to

the shorter life of the obese. Only 10 of the 33 persons between fifty-five and sixty-four were sixty or over.

These persons were referred to us chiefly by the departments of general medicine, orthopedics, arthritis, general surgery, or gynecology to which they applied because they were suffering from cardiac, gastro-intestinal, respiratory, menstrual, or other gynecologic, joint or other symptoms. These factors, and not vanity or realization of the danger of obesity, brought them to the clinic. The weight-bearing parts of the body, the cardiorespiratory system, the pelvic organs, and many other parts suffer as a result of the obesity. The relief with loss of weight was frequently surprisingly great. Indeed, the gratitude alone of the person relieved fully repays the relentless efforts required of the physician to accomplish the desired results.

Approximately 85 per cent. of the patients were 20 to 100 pounds above standard average weight. Fourteen per cent. were more than 100 pounds overweight. Expressed as percentages of the standard weight, 87 per cent. were 20 to 100 per cent. overweight. Treatment is still in progress in so large a proportion of these persons that results cannot be satisfactorily given. It is enough to say that losses of 50 to 70 pounds have been secured in many cases and a few have lost 90 to 100 pounds, or even more. The treatment used has been a combination of diet and exercise. The principle underlying the diet has been adequate protein and minimal carbohydrate and fat, especially carbohydrate. The specific dynamic action of protein has been believed in, but not specifically employed on account of the necessarily attendant large fat ingestion. In the beginning of treatment a diet of roughly 750 calories was prescribed, including 70 grams of protein. The diet was increased whenever very rapid loss of weight, strength, or energy indicated the need of it, but this seldom occurred. At each revisit the record of food taken was secured and recorded as grams of carbohydrate, protein, and fat. The total calories reported taken varied between 400 and 1000 calories in 69 per cent. of the cases. The question can properly be raised as to whether more food was ingested than the amount reported. Some evidence leads one

to believe that in some cases 20 to 30 per cent. more was taken. But this cannot be proved. When a 1200-calory diet was prescribed and reported as taken, loss in weight was greatly slowed up or stopped in the majority of instances.

In the first week of the 750-calory diet the average weight-loss was $5\frac{1}{2}$ pounds. Thereafter the weekly loss averaged 1 to $1\frac{1}{2}$ pounds, and where more than 2 pounds per week were lost weakness and lack of energy soon appeared. The tendency to lose weight more rapidly at first and less rapidly after several weeks was generally evident.

Water intake was not restricted, but patients were urged to take 1800 to 2000 c.c. of water in addition to other fluids desired. Salt intake was restricted where renal functional tests showed the need of it. Protein intake was occasionally restricted where nitrogen retention was present.

Exercise was prescribed not so much to secure greater food utilization as to train relatively unused muscles for the greater activity necessary later to maintain weight at its proper level. That is, we tried to educate the individual to a more prodigal use of muscular energy, and in a certain proportion of instances this was definitely attained. The exercises prescribed were walking and gymnastics of the simplest type, aimed at strengthening the back, abdominal, and lower extremity muscles. We were surprised at the relative ease with which backache was relieved.

It is necessary for the physician to see the patient frequently and go searchingly into his life during the intervals between visits. A firm, helpful manner is essential. Some encouragement is needed, but the patient must be made to realize clearly the necessity for perseverance and self-reliance.

Several interesting observations were made of clinical features which are attendant upon obesity. These were the basal metabolic rate, the blood-pressure and its changes under treatment, the hemoglobin, and the blood-sugar.

The basal metabolic rate, as pointed out by many observers, is usually normal. In our series about 6 per cent. were below minus 15 per cent. These persons did well on small doses of thyroid-gland extract. Their loss of weight was not satisfactory

until glandular treatment was started. Those showing a normal metabolic rate were not appreciably helped by thyroid medication.

The blood-pressure studies were very interesting. Table III shows the diastolic and systolic pressures at the time of admission to the clinic. The lower line of the table of systolic pressures indicates the average increase in pressure of healthy adults as they grow older. The upper line is drawn in as worked out through the courtesy of the statistical department of the Metropolitan Life Insurance Company and is founded upon the

TABLE III

Systolic Pressures

	10–14	15–19	20–24	25–29	30–34	35–39	40–44	45–49	50–54	55–59	60–64	65–69
200–						1	3		4	3		
190–199							2			2	1	
180–189						1	1	1	1	1	1	
170–179						1	1	2	1	1		
160–169				2	1	3	2	3	2	1	2	2
150–159				1	1	3	2	3	4	4	1	2
140–149			2	2	4	8	6	6	7	5	2	2
130–139		1	4	2	7	6	8	2	4	4	1	
120–129	1	1	4	9	6	4	5	8	6	2		
110–119		4	2	9	6	8	2	1		1		
100–109	1			2	2	3	1					
90– 99		1										
On or above mean	1	1	8	11	15	24	25	17	22	19	7	6
Below	1	6	5	16	12	14	8	9	7	5	1	

Diastolic Pressures

	10–14	15–19	20–24	25–29	30–34	35–39	40–44	45–49	50–54	55–59	60–64	65–69
On or above mean	1	2	6	11	12	13	18	16	10	10	5	3
Below	1	5	7	15	14	12	8	8	14	11	3	3

	10–14	15–19	20–24	25–29	30–34	35–39	40–44	45–49	50–54	55–59	60–64	65–69
130–							1		1			
120–129					1		1		1	1		
110–119						2	2		1	3		
100–109						2	1	1		1	1	
90– 99			2	4	6	3	5	7	7	5	4	3
80– 89		2	1	7	5	6	8	8	7	7	2	1
70– 79	1	1	5	10	10	9	6	6	6	3	1	1
60– 69	1	4	2	5	4	3	2	2	1	1		1

mathematical theory of least squares. The observations are too few in number to give the line the value of great accuracy, but it is approximately accurate and indicates a very definite tendency to increased systolic pressure. The line in the diastolic pressure table is that of the best obtainable figures for rise in pressure with increase in age of healthy normal individuals. No mean line for this group was secured, but there seems less tendency for this element in pressure to increase.

Under treatment the blood-pressure tends to fall and remain at a lower level as long as the weight is falling or steady. When rise in weight occurs, a rise in blood-pressure soon follows. In some instances, chiefly those with a high and fixed diastolic pressure, the systolic pressure also remains high and is unaffected by fall in weight.

Secondary anemia, usually of mild degree, occurs frequently with obesity. Fifteen per cent. of our cases showed hemoglobin readings under 80 per cent. Treatment of the anemia improved the subjective symptoms of the patients, and seemed to accelerate the loss in weight.

The possible relationship between obesity and diabetes has been emphasized by Joslin, and others have recently shown the same facts that we have worked out with this material. Twenty-four per cent. of our patients showed fasting blood-glucose tests reading above 0.12 per cent. at the time of admission. The tests were made by the modified Benedict method. A few glucose tolerance curves made on obese persons in the arthritis department take a position between the average normal curve and the curves lying definitely in the diabetic zone.

The solution of the problem of obesity seems to lie in accurate metabolic studies. To date the reported studies do not sufficiently explain the fundamental differences of the obese from the thin or average person. Water balance and carbohydrate, protein, and fat metabolism studies are under way in many centers. Before long we should have a more rational understanding of the underlying causes of obesity. In the light of what we already know with fair certainty we can say that many of the so-called obesity "cures" are neither cures nor safe.

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WHAT IS A CHRONIC APPENDIX?

AMONG some members of the medical profession there seems to be held the impression that making a diagnosis of chronic appendix is equivalent to a confession of ignorance. This, of course, is far from the truth, but a careful study is always necessary before this diagnosis should be made, and if the diagnostic procedures are carried out properly, there will be more satisfaction in treating such cases not only from the viewpoint of the patient, but of the doctor as well. In replying to the question as to what constitutes a chronic appendix, answers from a pathologist, a surgeon, or internist, and a roentgenologist would vary greatly.

A chronic appendix is one in which there has developed an atrophy of the glands and lymphoid tissue with a subsequent replacement fibrosis, this change frequently following an acute inflammatory reaction. The fibrotic changes may or may not have caused obstruction or obliteration of the lumen of the appendix, but if this has occurred there may have developed a cystic dilatation. Cystic dilatation of the appendix may be caused by bands or adhesions as well as by an acute inflammatory reaction. Fecal concretions, foreign bodies, intestinal parasites, congenital bands, and adhesions often cause chronic disease of the appendix.

With this brief description of the pathologic changes in mind, the internist recognizes two main types of complaints caused by a chronically diseased appendix. From one group of patients there is obtained a history of one or more severe, or mild but

typical attacks of acute appendicitis which subside without surgical interference. The chronic persistent symptoms do not, as a rule, follow directly after an acute attack, but appear gradually, may be persistent or intermittent, and may be interrupted by an occasional acute exacerbation of varying intensity. Differing from these patients is the group from whom there cannot be elicited the history of typical acute attacks and in whom the symptoms are of slow gradual development. These symptoms are most frequently caused by the pathologic changes which interfere with function. Such are bands, adhesions or fecal concretions. Some of these patients suffer subsequent acute attacks, but the symptoms usually precede the acute attacks and are apt to be less severe and of longer duration.

The most trustworthy and characteristic symptom of a chronic appendix is a dull, heavy or burning pain in the right lower quadrant. It may be constant or intermittent, frequently it is worse in periodic attacks lasting a few days or weeks with rather long periods of remission. The most typical pain, however, is constant, even though not always severe. Pain in the epigastric and umbilical region when due to a chronic appendix is usually sharp or crampy.

Nausea, vomiting, sour eructations, belching, distention after meals, and constipation are complained of frequently by patients, whose symptoms are due to a chronic appendix, but these complaints are so common that there is nothing distinctive or characteristic of the condition under discussion. However, if these symptoms appear for the first time after a definite acute attack of appendicitis and persist, they have significance and assist in making the diagnosis.

The most typical physical sign of chronic appendicitis is tenderness in the right lower quadrant. The exact location of the tenderness varies, depending on the location of the diseased organ. A retrocecal appendix will cause tenderness in a different area than will an appendix with the tip fixed in the pelvis. The degree of tenderness also differs at times, though it is nearly always present to some extent.

The history, then, of a definite, dull heavy pain in the right lower quadrant associated with real tenderness in the same area is presumptive evidence of a chronically diseased appendix. If there have been typical acute attacks either mild or severe, characterized by headache, nausea, vomiting, chill, fever, and localizing pain in the right lower quadrant, the presumptive evidence becomes stronger. The differential diagnosis must consider the possibility of a pathologic gall-bladder, renal or ureteral calculus, kinking or stricture of the ureter. Acute diverticulitis, superficial neuralgia, and disease of the pelvic organs in females must be thought of as well.

If a roentgenologic examination is carried out properly on those cases in which the appendix is suspected of being the cause of symptoms, it is possible to attain a very high degree of accuracy in diagnosis. During the course of a complete gastro-intestinal *x*-ray examination, the stomach, duodenum, and colon may be shown to be free of pathologic change. Since it is possible to visualize the appendix in 65 to 75 per cent. of those persons not past middle life, there is most valuable direct evidence to be gained. It was believed some years ago that the appearance of barium in an appendix was abnormal, but this assumption is no longer tenable. Direct visualization of the appendix being possible in most individuals, information is gained regarding position, size, filling, and emptying and the reaction of the patient to direct pressure.

The normal appendix is visualized as coming off from the inner and posterior portion of the cecum, below the ileocecal valve. It is freely movable, fills regularly and empties synchronously with the cecum and ascending colon. Abnormalities of position are noted frequently as the appendix may be retrocecal and extend some distance upward, or may be fixed well over the brim of the pelvis. Occasionally an unrotated or partially rotated cecum will cause an appendix to be in an abnormal location. The average appendix is 6 or 8 cm. long, though frequently an appendix double or half this length is seen. The size of the appendix has very little to do with pathologic changes. Normally the barium-filled appendix is seen as a

shadow of equal density and regular outline. If concretions, fecaliths, adhesions, or bands are present the barium column may be irregular or beaded in appearance. Cystic dilatation is seen as a club-shaped or bulging shadow as the lumen of the appendix becomes dilated in different portions. Appendices which are kinked, coiled, or twisted are seen frequently and are abnormal if the deformity is persistent. The normal appendix is freely movable and fixation of the appendix is a very valuable diagnostic sign.

The foregoing *x*-ray evidence is of distinct diagnostic value, but the two most definite signs of disease are gained from a study of the emptying time of the appendix and the reaction of the patient to direct pressure over the visualized appendix. The normal or average appendix is free of barium not long after the cecum and ascending colon have evacuated the barium meal. Occasionally a large part or the whole of the barium meal is entirely evacuated from the body before the twenty-four-hour examination is made. This is the case neither frequently nor rarely, but happens occasionally. Usually the cecum and ascending colon are entirely free of barium between the twenty-fourth and forty-eighth hours after ingestion of the opaque meal and the appendix is emptied a short time thereafter. There is evidence to show that an appendix which retains barium after the entire colon has evacuated the barium meal, is definitely diseased. It seems much more logical to compare the emptying time of each appendix with the emptying time of its own colon than to consider that at any predetermined fixed hour retention becomes a diagnostic factor. An appendix filled with barium at the forty-eight-hour examination if the remainder of the colon is empty is of more significance than is an appendix filled at the seventy-two-hour period if the transverse and descending colon still contain a part of the meal. Additional evidence regarding the ability of the appendix to empty can be gained by administering a laxative to a patient whose colon is free of barium but whose appendix still retains the barium. Failure of the appendix to empty after catharsis is evidence of a more severe damage to function.

Thus far in the roentgenologic examination the evidence may be gained entirely from a study of films. The examination of the barium-filled appendix under the fluoroscope with the patient supine upon a horizontal table, is an indispensable feature of any gastro-intestinal investigation. It is during such a procedure that direct pressure with the gloved finger or thumb is applied over the various parts of the gastro-intestinal tract to determine the presence or absence of tenderness. Tenderness over the appendix is not enough to warrant a positive diagnosis, but again is of comparative value. Pressure over or tension upon the sigmoid or other parts of the colon is usually discomforting. Tenderness over the appendix to be diagnostic must be a definitely greater degree of tenderness than the same pressure or tension elicits over other areas of a normal colon. It is also important to be sure that tenderness over a loop of the transverse colon in close approximation to the cecum should not be confused with tenderness over the cecum or appendix itself.

In order of importance, the diagnostic data of a roentgenologic examination are:

1. Failure of the appendix to empty synchronously with the colon.

2. Definite tenderness over the appendix greater than over any other part of the normal colon.

3. The evidence of abnormality of position, size, and mobility.

The failure of the appendix to empty as the colon empties is abnormal. The degree of appendiceal retention gives a good deal of information as to the extent of damage done. Likewise, the demonstration of tenderness with direct pressure over the visualized appendix is much more satisfactory than any other method. The judgment of the examiner in evaluating the reaction of the patient is also of the utmost importance.

Once the diagnosis of a chronically diseased appendix is made, the proper treatment is clear; surgical removal always being advisable unless there is some clear contraindication. A small, though definite percentage of chronic appendices suffer acute exacerbations and demand immediate surgical care, so

that temporizing with the situation after the diagnosis is assured is dangerous. As is frequently the case, immediate operation may not be expedient. Financial burdens, necessary household or business duties, or other considerations may necessitate delay. In this event the patient should be warned against going to any location where an acute attack could not be treated suitably. At the same time a bland diet with a soft bulky residue, lubrication of the colon with mineral oil, avoidance of drastic catharsis and all efforts to improve the general health should be insisted upon.

The surgical removal of a symptom-producing, chronically diseased appendix results in a uniform and practically perfect result. Those cases which are classed as being unsatisfactory are almost negligible. Failure to cure should not be considered so much a surgical failure as an error in diagnosis. Gibson[1] in 1920 reported the end-results in a large group of patients operated upon for chronic appendix. These results were surveyed most critically, judged, and found lacking in perfection of result in too large a proportion of cases. It was found that there were only about 60 per cent. of the results which were satisfactory, errors in diagnosis and surgical technic together with an improper selection of cases largely being responsible for the poor showing. Correcting these factors resulted in a most satisfactory and encouraging report[2] from the same source four years later, in which the satisfactory postoperative results had increased to 85 per cent., an improvement of note. Deaver and Ravdin[3] likewise summarized the end-results in 500 cases of chronic appendix which had been operated upon and found that 83 per cent. of the patients were completely relieved of their symptoms. In both of these reports the occurrence of acute attacks was considered of the utmost importance in making sure the diagnosis and in addition the necessity of careful and thoroughly complete examinations was stressed.

Today the operation for a chronic appendix is looked upon not only as a surgical procedure to remove a definitely diseased organ, but of equal importance is the exploration of the other intra-abdominal and pelvic organs. The day of the small, neat,

cosmetic scar in the right lower quadrant is past. A commonsense incision is made through which an adequate investigation of the abdominal cavity can be carried out. This is done not only to permit exploration, but also to enable the operator to correct any other pathologic condition encountered. This type of operation has forestalled many of the unfortunate results of older days in which failure to cure was attributed to unsuccessful surgery instead of properly placing the blame upon unrecognized pathology. The health claim department of one of the large insurance companies states that it is almost an axiom that claims for illness caused by duodenal ulcer are preceded by a claim for operation for chronic appendix. It is certainly a fact that many persons still are operated upon for a supposed chronic appendix whose symptoms are due to other pathologic causes.

The appended tables illustrate strikingly the satisfactory and unsatisfactory after-results of operation for chronic appendix. The only selection of the cases studied and tabulated was that they comply with the following requirements: (1) A record of complete history and physical examination, *x*-ray study and other special investigations as indicated; (2) a complete report of the operative findings, and (3) no case was considered which had not been operated upon more than a year previous. The individuals in both groups are comparable from a financial and social standpoint and most of the operations were performed in the same hospitals by the same surgeons. Tables I and II give a detailed statement of each case while the summary table compares the two groups. Group I is made up of younger persons with a larger proportion of females. In this group the history of acute attacks and the complaint of a definite pain in the right lower quadrant associated with tenderness is more common. The roentgenologic examination in Group I was carried out much more intensively and was extended over a longer period of time. In no case in this group was an *x*-ray diagnosis of chronic appendix made in which the two following criteria were not present: (1) Definite and prolonged appendiceal retention of barium after the rest of the colon was free of the opaque meal; (2) definite tenderness

TABLE I

NO.	SEX	AGE	PAIN	DURATION	ACUTE ATTACKS	OTHER SYMPTOMS	PHYSICAL EXAM.	X-RAY or FLUOROSCOPIC EXAM and DIAGNOSIS	OPERATIVE-FINDINGS	TIME POST-OPERATION
1	F	27	Right lower quadrant	12 months	1 Typical	None	Tender RLQ	Appendix beaded kinked and tender. Retains Barium 72 hours. Remainder Gastro Intestinal Tract neg	Appendix 7cm long, thinned out, obliterative type. Definite chronic app	Less digestive disturbance, no pain, general health much better 5 yrs
2	F	25	Epigastric	6 "	" "	Slight nausea moderate constipation	Definite tenderness RLQ	Appendix club shaped, adherent, very tender, retains Ba 72 hrs. Rem GIT neg	Appendix bound down, mid-portion; congested Definite Chronic app	Perfectly well 2 yrs
3	F	27	Dull, RLQ	24 "	Several Typical, mild	Frequent nausea & vomiting, sour eructates	Tender RUQ+LQ Liver palpable	Appendix filled beaded tender. 72 Ba retention Remainder GIT neg	Badly inflamed definitely diseased Chronic appendix	" " 4 "
4	F	23	Full, heavy, RLQ	6 "	1 Typical	Slight nausea	Slight tenderness RLQ No hy Ba retention	Appendix filled, tender, beaded Remainder GIT neg	Chronic appendix — many fecoliths	No Gastro-Intestinal symptoms 2 yrs
5	M	21	Dull, " " " "	" "	None	Sour eructations Heartburn	Thin ptotic type, definite tenderness RLQ	Appendix retains Ba 72 hrs. very tender. Remainder GIT negative	Appendix 9cm long, congested obliteration of tip	Perfectly well except slight constipation 3 yrs
6	F	23	" " " " "	12 "	"	Slight heartburn constipation	Tender RLQ	Appendix retains Ba 72 hrs; mobile, very tender Viscera atonic, otherwise neg GIT	Appendix bound down and mass of adhesions.	Perfectly well 5 yrs
7	F	20	Dull, aching " "	42 "	"	None	Liver palpable slight tenderness RLQ	Appendix retains Ba. 10 days. High fixation of Duodenum, otherwise neg GIT	Distal ⅔ of appendix dilated, constricted by band ½ in from cecum	3 "
8	F	22	LUQ and Epigastric	36 "	"	Sour eructations	Tender RLQ	Appendix filled, kinked tender 7 days. Second portion of Duodenum drawn to right, otherwise neg GI Tract	Lane Kink Harris Band chronic appendix	100% cured 3 years
9	F	22	RLQ sharp	9 "	3 Typical Subacute	None	" RLQ	Appendix filled 3 days beaded, tender, otherwise neg GI Tract	Chr appendix membranous pericolitis	Well " "
10	F	27	Dull RLQ + Umbilical	2 "	None	Bloated after meals Sour eructations	Def. tenderness RLQ	Appl filled tender 96 hrs Duodenum drawn to right, otherwise neg GIT	Definite chronic appendix	Perfectly well " "
11	F	18	Slight RLQ + Epigastric	24 "	"	Slight nausea, vomiting moderate heartburn	Negative	Appendix filled 5 days very tender	Chronically inflamed, adherent, with several bands of cecum	" " " "
12	F	18	Epigastric 1 hour after meals	2 "	"	None	Tender RUQ+RLQ and epigastrium	Marked pylorospasm, appendix retains Ba 72 hrs, very tender otherwise neg GIT	Definite chr appendix chronic cholelithiasis	" " 1½ "
13	F	20	RLQ	4 "	3 Typical Mild	Frequent nausea, moderate sour eruct.	Ptotic type Tender RLQ	Appendix tender, retains Ba 6 days; otherwise neg GIT tract	Long, irregular, thickened congested retrocecal chr appendix	" " " "
14	F	22	Epigastric RLQ and LLQ more RLQ	" "	None	Pain worse with menstrual period	Ptotic type Tender RLQ+LLQ	Appendix filled, tender 72 hrs; otherwise neg GIT	Definite chr appendix	Very much improved some indigestion with periods 3 years
15	M	31	Dull RLQ	3 "	"	Epigastric distress after meals	Tender RLQ	Appendix filled tender 5 days, otherwise neg GIT	Retrocecal, adherent, inflamed chr appendix	Perfectly well 4 years
16	F	20	" "	" "	1 Typical	Sour eructations	" "	Appendix filled, tender, beaded, movable 7 days; otherwise neg GIT	8 cm long, kinked, adherent	" " 2 "
17	F	32	Sharp and dull RLQ	60 "	Several rather severe typical	Occasional nausea Vomiting	Slight tenderness RLQ	Appendix filled, tender 6 days otherwise neg GIT	Acute gangrenous appendix removed Acute attack 6 mo after exam	" " 1 "
18	F	24	Aching RLQ	12 "	2 Typical	None	Tender RLQ	Appendix beaded, tender 72 hrs; otherwise neg GIT	Definite subacute appendix	" " 2 "
19	M	26	" " " "	4 "	None	Heartburn and sour eructations	Slight tenderness RLQ	Appendix filled, tender 7 days; otherwise neg GIT	Thickened long, chronically diseased appendix	" " 1½ "
20	M	21	RLQ dull	1 "	"	None	Tender RLQ	Appendix fixed movable tender 72 hrs; otherwise neg GIT	Thickened kinked injected appendix Site of previous inflammation	" " 1 "
21	F	18	Dull, aching RLQ	8 "	2 Typical Mild	Slight nausea	" "	Appendix filled, kinked, tender 72 hrs; otherwise neg GIT	Thickened injected chr app.	" " " "
22	F	21	Dull, worse when tired RLQ	18 "	3 Typical Mild	None	" "	Appendix filled tender 72 hrs, otherwise neg GIT	Chronic appendix	" " " "
23	F	24	RLQ and R Lumbar	1 "	1 Typical Mild	"	Tender RLQ and LLQ	Appendix fixed tender, filled 72 hrs otherwise neg GIT	Bound down & obliterated Left Cystic ovary	" " 3 "
24	F	18	Dull RLQ	7 "	2 Typical Mild	"	Definite tenderness RLQ	Appendix beaded tender, filled 96 hrs otherwise neg GIT	Kinked adherent chr app	" " 1½ "
25	M	19	Umbilical	3 "	Severe acute typical	"	Negative	Appendix tender, filled 72 hrs, otherwise neg GIT	Large turgid mucopurulent appendix	" " " "

24	F	18	Dull RLQ	7 "	2 Typical Mild	"	Definite tenderness RLQ	Appendix beaded tender, filled 96 hrs otherwise neg GIT	Bound down & obliterated Left Cystic ovary	" "	3 "
25	M	19	Umbilical	3 "	Severe acute typical	"	Negative	Appendix tender, filled 72 hrs, otherwise neg GIT	Large turgid mucopurulent appx	" "	1½ "

TABLE II

NO	SEX	AGE	PAIN	DURATION	ACUTE ATTACKS	OTHER SYMPTOMS	PHYSICAL EXAM.	X-RAY or FLUOROSCOPIC EXAM and DIAGNOSIS	OPERATIVE FINDINGS	TIME POST-OPERATION
1	F	34	RUQ 2 hrs after meals	24 months	1 mild Typical	Occasional vomiting Vomited blood once	Liver palpable, tender, tender RLQ	Negative organic disease GIT Chr Appendix	Gall bladder normal Harris band-appendix buried in adhesion Pelvic organs OK	Symptoms about the same General condition same 5 yrs
2	F	36	RLQ	14 "	None	Occasional slight jaundice	Tender RLQ	Appendix tender, movable cecum tender, otherwise neg GIT	Chronic appendix Cyst of right ovary	Complete relief 1 yr
3	M	30	" " "	36 "	2 Mild Typical	Loss of 20 lbs	Tender RLQ Slight rigidity	Pylorospasm - Chr Appendix, otherwise negative	Appendix long coiled, prececal Pathological report - normal appendix	" " "
4	M	28	" " "	1½ "	None	None	Tender RLQ	Appendix not seen marked tenderness over cecum	Gall bladder Pelvis OK Omentum adherent to peritoneum App adhnt to om	No relief 2 yrs
5	M	20	" " "	5 "	"	Distention bloating after meals	Tender over colon	Appendix kinked, tender, otherwise negative	Acute gangrenous appendix 3 months after exam	Partial relief Symptoms less severe 1 yr
6	M	43	Epigastric	6 "	(Severe 2 mild typical attacks	None	Tender epigastric and RLQ	Appendix tender, otherwise negative	Chronic appendix	Partial relief Later exam revealed 2 of ureteral calculi 2 yrs
7	F	22	Cramplike RLQ	18 "	None	Nausea and epigastric distress	General abdominal tenderness worse RLQ	Appendix fixed, tender, otherwise negative	Appendix distorted, bound down, contains concretions Exploration other neg	Partial only Symptoms about same 3 yrs
8	F	27	Cramplike umbilical	3 "	Mild Typical	Occasional vomiting Cramplike abd pain	Epigastric tenderness	Duodenum pulled to right Appendix tender, otherwise neg	Kinked appendix Exploration otherwise negative	No relief Complete exam subsequent to operation showed no org lesion
9	M	28	RLQ	3 "	None	Vomiting dull aching pain worse 2 hrs after meals	Very tender RLQ	Appendix very tender, otherwise neg	Tip of appendix fibrotic Exploration negative	Complete relief 6 years
10	M	33	Epigastric	6 "	"	Weak spells, pain in epigastrium	Very tender RLQ	Appendix very tender, otherwise OK	Appendix kinked, thickened Exploration negative	No relief - Had second operation possible duodenal ulcer, no ulcer found 2 yrs
11	F	26	LUQ	6 "	"	Belching distention dizziness	Negative	Appendix beaded, tender at 72 hrs Otherwise neg	Retrocecal appendix - Harris band Exploration negative	Partial relief - has gained weight - less indigestion 1½ yrs
12	M	40	Epigastric	8 "	"	Dull epigastric pain lasting 1 hr after meal	Tender RLQ	Appendix fixed, tender - otherwise neg	Definite Chr App Explor neg.	Complete relief 1 yr
13	M	23	Burning RLQ	For years	1 Typical Severe	Nausea off-on for years - Pain in RLQ	" " "	" " "	Subacute Appendix	Improving all the time since operation 1 yr.
14	M	56	LUQ	6 months	1 Typical - 6 mo after exam	Vomits occasionally cramp. pain LUQ	" +RUQ	Pylorospasm - App very tender; otherwise OK	Chronic appendix with walled-off abscess Operation 6 mo after exam	Complete relief 6 yrs
15	F	46	Epigastric RLQ	12 "	None	Vomiting Pain RUQ, RLQ	" " "	Appendix filled and tender at 96 hrs X-ray gall bladder - pos cholelithiasis	Chr appendix and cholelethiasis	" " 1 "
16	M	30	" " "	1 "	"	Epigastric pain occasional vomiting	Epigastric tenderness LLQ	Questionable pyloric ulcer 2 Neg GIT Series Duodenal ulcer Chr app (drag)	Chr appendix - exploration negative	" " 2 "
17	F	36	RLQ	6 "	"	None	Tender RLQ	App tender, filled, otherwise neg	Chronic appendix	Partial relief only Pt pain in RLQ - 1½ yrs

of the appendix visualized under the fluoroscope with the patient in the supine position. The *x*-ray examination in Group II did not, as a rule, extend beyond the twenty-four-hour period and was less complete. As would be expected, in Group I the operative findings were much more definite and the results obtained were perfect from the standpoint of both physician and patient in 92 per cent. of the cases and satisfactory in the remaining 8 per cent. The end-results in both groups were noted only after repeated observations following the operation.

Summary.—There is a rather general impression among the members of the medical profession and also among laymen that a diagnosis of chronic appendix is equivalent to a confession of ignorance, and, therefore, unjustified. This is due largely to the rather inadequate and unsatisfactory diagnostic procedures with a loose handling of the term "chronic appendix," coupled with an unsatisfactory type of operation upon patients so diagnosed. It has been shown[1, 2, 3] that in large groups of patients who are carefully examined before being operated upon by competent surgeons, there is obtained a very satisfactory end-result. If in addition a roentgenologic examination is carried out properly, thus aiding diagnosis and the proper selection of cases for operation, the chances of cure are again enhanced.

Conclusion.—A chronic appendix is more common in young adults, typically causes a dull pain in the right lower quadrant associated with definite tenderness. Roentgenologic examination aids in the diagnosis in at least 65 to 70 per cent. of the cases and gives valuable diagnostic assistance, the two most trustworthy findings being (*a*) the retention of barium in the appendix after the remainder of the colon is free of the opaque meal and (*b*) the eliciting of tenderness by exerting pressure over the appendix visualized under the fluoroscopic screen. The end-results after surgical removal of such appendices thus shown to be diseases are more nearly perfect than obtained by any less thorough and complete examination.

SUMMARY OF TABLES I AND II

	1. *Sex*	2. *Age*	
Table I:	Males, 5–20%	Youngest, 18	
	Females, 20–80%	Oldest, 32	Average, 20.3
Table II:	Males, 10–56%	Youngest, 20	
	Females, 7–44%	Oldest, 56	Average, 32.8

	3. *Pain—Location.*	*Dull.*	*Sharp.*	*Total.*	*Duration.*	*Average.*
Table I:						
	R. L. Q., 21–84%	15–71%	2–10%	81%	Longest, 60 mos.	12.3 mos.
					Shortest, 1 mo.	
Table II:						
	R. L. Q., 10–58%	...	...	..	Longest, 1. "for years"	
					2. 36 mos.	
					Shortest, 1 mo.	9.6 mos.

	4. *History of Acute Attacks*	5. *All Other Gastro-intestinal Symptoms*
Table I:	14–56%	None, 10–40%
		Other symptoms present, 15–60%
Table II:	6–36%	None, 3–18%
		Other symptoms present, 14–72%

	6. *Tenderness (Definite)*	7. *Roentgenologic Examination*	8. *Diagnosis*
Table I:			
	R. L. Q., 22–88%	Longest retention of barium, 10 days*	Chronic appendix, 22–88%
		Average, 4 days	Chronic appendix and other pathology, 12%
Table II:			
	R. L. Q., 11–64%	Longest retention of barium, 4 days	Chronic appendix, 16–93%
		Average, 25 hours	Chronic appendix and other pathology, 1–7%

	9. *Operative Findings*		10. *Results*	
Table I:				
	1. Chronic appendix only,	21–84%	1. Cured (complete freedom from symptoms),	23–92%
	2. Chronic appendix and other pathology,	4–16%	2. Satisfactory. Practically no symptoms,	2– 8%

Table II:

1. Chronic appendix alone, 11–64%		1. Cured,	8–48%	65
2. Chronic appendix and other pathology, 6–36%		2. Partial: (*a*) Satisfactory,	3–17%	
		(*b*) Unsatisfactory,	2–12%	35
		3. No relief,	4–23%	

11. *Time Postoperative*

Table I: Longest, 5 years; Shortest, 1 year; Average, 2.5

Table II: Longest, 6 years; Shortest, 1 year; Average, 2.2

* At operation twenty-two days after *x*-ray examination, an appendix with barium was found in one patient.

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CHEST PAINS

ANGINA pectoris is merely a symptom, but an ominous one, to be sure. In the minds of most of us the term arouses a picture peculiarly definite: We see a man past middle-life seized by a pain or crushing oppression across his sternum that exhausts his store of similies to adequately describe; a pain that radiates into his left arm, holds him motionless, afraid even to breathe, and accompanied by a sense of impending death, compared with which the bodily suffering sinks into insignificance.

As a matter of fact, this is more of a text-book picture than an actual experience, for we see only rarely this symptom complex in its entirety, but we do see all approximations to it. What do we mean by the term? Perhaps as good a definition as another would be *pain or equivalent discomfort in certain nerve distributions, supposedly originating in the heart or aorta.*

The nerve distributions in which the pain is felt are derived usually from the lower cervicals and upper dorsal segments of the cord, less commonly from centers higher up or lower down; hence the pain is felt characteristically in the upper chest, arm, and lower neck, especially to the left, and less often in the lower anterior chest, the back, the abdomen, the upper part of the neck, the jaws, and the head.

* For several years we have been especially interested in the subject of chest pains because of the large number of cases which we have seen in the office. Each of us has read papers on various phases of the subject with the intention of writing such an article as the present one. But Dr. Meara died in October, 1927, before we had completed our plans. In this paper I have incorporated verbatim as much as possible from Dr. Meara's manuscripts in an attempt to preserve the charm peculiar to his style. (C. M. G.)

Here, then, is our problem: Pain in the areas specified; is it angina pectoris in the sense of being of cardiovascular origin, or is it not? A differential diagnosis is the first step toward treatment. We have localized the pain to certain nerve distributions. What part of the nervous apparatus is the site of such irritation as to give rise to pain?

It may be due to an *irritation of the nerve centers from direct or indirect excitation; of the nerve-roots; of trunks or endings.*

The *irritation of the ganglion cells* occurs in herpes zoster. When the lesion is confined to the upper dorsals of the left side one can readily see how, during that period of days preceding the eruption, in which neuralgia of the nerves affected is characteristic, both patient and physician may be alarmed in no small measure. The persisting of the pain and its irrelevancy to effort should arouse suspicion, which, of course, is confirmed with the appearance of the eruption. *Tabes dorsalis*, with its lightning pains, may simulate an angina, perhaps most commonly of the abdominal type, that type so commonly beginning with epigastric pain.

In a similar manner pain may be felt in the area of angina pectoris by *pressure upon or irritation of the posterior roots* by new-growths in the spine or cord, by a spondylitis, a part of a rheumatic affection, or by lesions in the vertebræ—tuberculous, pyogenic, syphilitic. It is true that if we give heed, the character of the pain, its provocation, the local examination, the *x*-ray, and concomitant symptoms should readily dispel the illusion of angina; if we only give heed!

Again *pressure upon or irritation of the nerve-trunks* may simulate angina. We have vivid recollection of a case of cervical rib that fooled a very excellent clinician. It is to be recalled that the supernumerary rib carries up over it the strands of the brachial plexus and the subclavian artery. When, with advancing years or illness, the muscles and tissues lose tone and resiliency the brachial plexus is stretched over the rib and irritated in the process; the result is pain in the arm and pectoral region, which, especially when confined to the left, readily suggests angina; but note that the subclavian is carried up by the

rib, too, and then it pulsates, like a huge distended carotid, for which it is often mistaken, and pressure here is painful and the pain is grossly exaggerated by movement of the arm, and it is very continuous. Do not forget that failure to feel the rib or to see it in the *x*-ray plate may be due to the fact that it is not an ossified rib, but its fascial representation that we have to deal with. *New-growths*, especially common as metastases into the axilla, or retraction of scar tissue after radical operations for carcinoma of the breast may simulate it and there is no reason why a patient who has had a carcinoma of the breast should not also have angina pectoris. There may be a period after the tumors are palpable when a differentiation is not easy, so we should not lightly or hastily settle the matter in our own minds. *Neuritis* from any cause may distribute pain through the anginal area. We will not further elaborate, as our wish is merely to widen the field of your observations.

The pain may originate in *somatic nerve-endings, e. g.*, in cases of myositis affecting the muscles of the chest, pectorals, and intercostals, or those of the neck and arm. The pain may originate in a lesion of the rib; lues, tuberculosis, neoplasms, infection, trauma, and fracture; or it may originate in a neoplasm of the soft tissues of the chest.

Here are pitfalls enough, but a little mindfulness and a little experience protect us from most of the humiliations that carelessness invites.

When we have eliminated all these sources of direct irritation we have to consider the causes of *reflex irritation* within the province of which true angina pectoris lies. But not all reflex irritations of the cord segments that distribute to the anginal foci, if we may use such a term, originate in the heart and aorta. There are others that originate in the pleura from inflammation of that structure or a neoplasm. There are still others that originate from below the diaphragm; from the gall-bladder, the stomach, the pancreas, the appendix, the kidney, from peritoneal bands and adhesions. Just as stimuli originating in the heart and aorta and transmitted to their appropriate spinal segments, may, if intense, overflow up and

down the cord, giving rise to pain in somatic areas remote from the heart's representation in the cord, so can pain originating in these remote segments, conversely, overflow up or down the cord to irritate the centers representing the heart and give rise to pain in the heart's somatic representation, the anginal area. We will touch upon these later.

What is the nerve supply to the heart, the irritation of which gives rise to angina major or minor; the latter of which has been called *petit mal* of the disease? It is, of course, the cardiac plexuses, their distribution and their connections. We quote Quain. "From the cardiac plexuses at the base of the heart, nerves pass to the auricle and there join a plexus chiefly of non-medullated fibers, which is beset with numerous small groups of ganglion cells. This ganglionated plexus lies for the most part immediately beneath the pericardial covering of the auricles; but its branches penetrate into the muscle substance.

"Nerves are also given off from the cardiac plexuses, which, passing downward along the commencement of the aorta and pulmonary artery, reach the coronary arteries, and accompanying these in their course, form secondary plexuses (right and left coronary plexuses) around these vessels." From the coronary plexuses branches pass over the surface of the ventricles under the pericardium and a few small branches are directed upward to join the auricular plexus. "The nerve-fibers form a close plexus (ground plexus) amongst the muscular bundles, and from the terminal branches (fibrils) pass off to muscle-cells."

The nerves of the cardiac plexuses "are derived partly from the cerebrospinal and partly from the sympathetic system (more especially from the pneumogastric nerve and from the cervical and superior thoracic ganglion of the sympathetic nerve)."

The cardiac plexus, like the solar and hypogastric, is placed further forward in the visceral cavity than the ganglionated cords and furnishes branches to the viscera.

The cardiac plexus lies against the aorta and pulmonary artery where they come in contact, and is divided into two parts; the deep is seen behind the vessels and the superficial more in front. "The superficial cardiac plexus lies in the con-

cavity of the arch of the aorta, between the ligament of the ductus arteriosus and the right branch of the pulmonary artery." It has connections with the upper or superficial cardiac nerve of the sympathetic and the vagus of the left side. It ends in the right coronary plexus. The deep cardiac plexus is larger than the superficial; it lies behind the arch of the aorta, between it and the end of the trachea and above the bifurcation of the pulmonary artery. "This plexus receives all the cardiac branches of the cervical ganglia of the sympathetic nerve except the upper cardiac nerve of the left side. It likewise receives the cardiac nerves furnished by the vagus and by the recurrent laryngeal branch of that nerve, with the exception of the left cervical cardiac nerves. It connects with both the right and left coronary plexuses and with the deep superficial cardiac plexus."

"The right or posterior coronary plexus is derived from both the superficial and deep cardiac plexuses, the filaments by which it arises embracing the root of the aorta. It accompanies the right coronary artery on the heart. The left or anterior coronary plexus is larger than the right, and is derived mainly from the left half of the deep cardiac plexus. Being directed forward between the pulmonary artery and the auricular appendage it reaches the left coronary artery and subdivides into two principal portions, which accompany the primary divisions of that vessel."

Here, in these plexuses, originates the pain; but when and in connection with what pathologic lesion? At once we tread upon controversial territory. The pain is attributed to stretching of the muscles of the heart, causing pain like an overdistended bladder; but no such dilatation can be adduced by physical examination, and the heart has been observed roentgenologically during an attack of angina, with no evidence of change in the heart findings (Schmidt, Jour. Amer. Med. Assoc., March 25, 1922, p. 930); to cramp or spasm of the heart-muscles, hard to visualize in the intermittent contractions of a heartbeat; to neuritis or neuralgia, which in some instances may well obtain; to intermittent claudication of the coronaries, which

has had long and valorous championship, including Osler, and which the condition of the coronaries at autopsy makes so appealing; to myocardial ischemia, which means, of course, inefficient coronary circulation, local or general; but today we lesser lights lean hard upon the opinion of two eminent clinicians, Sir James Mackenzie and Sir Clifford Allbutt.

Mackenzie's theory is that angina pectoris is an expression of the exhaustion of the function of contractility. This exhaustion may come about from inadequate blood-supply, due to diseased coronaries, so narrowed as to obstruct the flow or so stiffened as to be incapable of that dilatation normal to increased effort, or to anemia, or to obstruction at the aortic orifice, or to high blood-pressure, or to malnutrition, bacterial infection, to overwork, worry, insomnia, to myocarditis, to adherent pericardium, to the rapid rates of paroxysmal tachycardia, flutter, and fibrillation. It is a good safe theory for the therapeutist to adopt; exhaustion demands rest and nobody disputes the value of rest and the decrease in danger by observing it.

Allbutt believes that angina is due to disease at the root of the aorta, especially that part just above the valve; that the lesion must be a deep, penetrating one or begin on the outside, as in syphilis, in the adventitia. He calls attention to the rich nerve supply to the sinuses of Valsalva and of the finding of the sensory corpuscles of Pacini or Vater in the outer layers of the adventitia and in the contiguous connective-tissue layers of this part, the root of the aorta; these are detached from the surface epithelium in the course of development and become sensory end-organs of the connective tissue of the adventitia, pericardium, and other investments along the bare vessels and the collar of the heart. It is irritation of these structures he holds responsible for the pain. This theory, too, has its practical applications, for it is certain that pathology of the aorta is associated with angina; what more severe pain than in luetic aortitis and this should lead us to investigate all possible sources of infection of the aorta and to take measures to lessen the irritation of the affected nerve structures. It leads, like Mackenzie's theory, to the bed and the rest it can afford.

Is there always structural pathology in angina pectoris and what is the nature of the pathology determined?

No, there is not always structural change in the heart of a man dying from angina pectoris. In some instances the most painstaking histologic examinations of the myocardium and the coronary vessels and of the aorta have failed to show any pathology. To say because no pathology was found that the case is not angina begs the question; angina, it is agreed, is a symptom-complex.

It is true, however, that in the vast majority of hearts that come to autopsy, there is a pathology which, as a rule, involves the coronaries.

That involvement of the coronaries should necessarily be followed by angina, however, does not follow; for all degrees of coronary scleroses and all degrees of coronary occlusion, even of main trunks, have been found in individuals who never had known angina. But this may be explained on the basis of Mackenzie's theory of exhaustion; *i. e.*, if a person with sclerotic coronaries lives within the reserve of his coronary circulation he does not have angina pectoris.

Reading autopsy reports on patients dying of angina pectoris, one is struck by the diversity of pathologic findings. As for ourselves, we have come to feel that the conclusions drawn from autopsy material are less that coronary diseases cause angina (though we would not deny the possibility) than that coronary disease lessens the chances of survival of those suffering from angina. Staring at diseased coronaries must make the divorcement of cause and effect in their relation to angina a difficult task; but the facts of the case are that diseased coronaries can at the most claim to be one of the causes.

Huchard reported sclerosis of the coronaries in 128 of 145 autopsies. Levine in a recent excellent article (Jour. Amer. Med. Assoc., September 16, 1922) says: "The outstanding fact that impresses one who studies the heart in the necropsy-room is that almost every patient with angina has more or less recent infarction of the heart, due to coronary closure," and further, "it seems to me that although an aortitis may be the underlying

cause of the pain, the prognosis depends on the condition of the coronary arteries." That statement approximates our own impressions.

If, indeed, most patients have a recent infarction of the heart, at least they do not die in attacks such as we attribute to embolisms of the coronaries, as a rule, nor do we get the history of these attacks in most of the patients; these attacks are clinically fairly distinct from the usual anginal attack. Upon this we will touch later. If infarction occurs, it must be due, in the majority of instances, to a gradual closure of the vessel.

Mackenzie gives the following pathologic conditions with which angina may occur: Aortic aneurysm, aortic insufficiency, coronary atheroma, myocardial degeneration, hypertension, and, of course, the coronaries *may* be implicated in each of these conditions, but he adds there may be *no* lesion whatsoever.

The common factor in all these lesions he finds in fatigue—impairment of the function of contractility.

So we come back again by way of pathology to the conviction that angina is not to be defined in terms of histologic pathology; but that the prognosis in any case does depend largely on structural pathology.

If the origin of the pain resides in hyperexcitation of the cardiac plexuses, the next task is to trace the paths of the stimuli to those end-stations where they express themselves as pain or other discomfort.

These stimuli, relayed through the cervical and thoracic ganglia, arrive at the cord by way of the gray rami communicantes; some maintain a direct route from heart to cord.

A more accurate knowledge of these routes is much to be desired. Head, on clinical grounds, would attribute the sensory supply of the heart to the first, second, and third dorsal segments, but the pain of angina is much more widely distributed than the areas supplied by the first three dorsals; but this is attributable, in part at least, to overflow up and down the cord. For lack of accurate anatomic knowledge it may be better to discuss radiation in terms of clinical knowledge, with

which we are better supplied. Mackenzie says the pain is usually felt in the distribution of the upper four dorsals and the seventh and eighth cervicals, but may be so low as the sixth dorsal, with pain in the epigastrium, or so high as the upper cervicals, with pain in the neck and back of the head.

A glance at Head's charts will show you that the storm-center in angina pectoris is, indeed, along the distribution of the first three dorsals, whose spinal segments Head believes to be directly connected with the heart. It is the first and third that distribute to the sternomanubrial junction, where the horrible oppression, compression, or pain is characteristically felt, while the second is distributed to the territory lateral to the first and third and conducts to the axilla, while the second supplies the inner aspect of the arm to the elbow and the first the inner aspect of the forearm from the elbow to below the wrist, while the third supplies the inner aspect of the arm anteriorly to the second. These three nerves present the great highway of anginal pain. Whether the segments contiguous to the first three dorsals are directly connected with the heart or not, they are affected in the degree of their contiguity.

The fourth dorsal supplies the skin in a circle embracing the trunk, just above the nipple, high in the axilla, and crossing the scapula behind, the fifth in the circle including the nipple, the sixth below the nipple and across the xiphoid, and these segments are so commonly affected that we can understand how such experienced observers as Allbutt should refer the center of pain to the upper and middle sternum, Sansom to the middle and lower sternum, and Gibson to the lower sternum more commonly than the upper. Sometimes the pain is felt over the body and apex of the heart—the true precordium; but as this area is supplied by the fourth and fifth dorsals, we can understand why pain over the heart is less characteristic than over the upper portion of the sternum and adjacent territory, especially to the left. In these areas of distribution Head has mapped out the points of maximum tenderness or pain, which lie outside the sternal area and cluster about the nipple, above, below, and inside. Commonly enough pain radiates to the

scapulæ and to the space between them, and with reason, for this area is supplied by the first five dorsals.

The overflow of stimuli is upward as well as downward and the segment next adjacent above is the eighth cervical. It supplies the strip along the anterior aspect of the forearm, the posterior central aspect of arm from axilla to hand and to the ulnar three fingers. It is common enough for an attack to start in this distribution, and it is not uncommon for the pain to be confined to this part, even for years, Mackenzie has said. The seventh cervical supplies the outer aspect of the arm and radial aspect of the forearm and thumb and first finger; the sixth cervical a patch over the deltoid; the fifth the biceps area; the fourth spreads out like a vest over the shoulder; the third like an old-fashioned stock, high in the neck.

It is in these outlying territories that difficulties of diagnosis begin to be established, but the overflow may not stop here; it may advance to the seventh, eighth, and ninth dorsals, and simulate any abdominal condition above the umbilicus and below the diaphragm as gall-bladder, gastric ulcer, duodenal ulcer, pancreatitis, renal disease, perforation, to mention only a few surgical conditions; mesenteric arteriosclerosis with infarction, lightning pains of tabes; to the tenth and eleventh and twelfth simulating appendicitis, ureteral calculus; to the lumbar, causing testicular pain; to the sacral plexus and by way of the pudic nerve to the anus.

In describing the cardiac plexuses above, it was stated that they were composed of fibers direct from the cord, by others from the ganglia, and by still others from the vagus. Study the connections and distributions of these ganglia and the vagi and you will understand why the phenomena of angina are so widespread and why they rock the very foundations of our being.

The superior cervical ganglion is connected with the first four cervical nerves, hence the pain over the occiput and in the distribution of the great occipital nerve; but more than that, it has connections with the twelfth cranial nerve, with the eleventh (spinal accessory), *through upper cervicals;* hence pain in the trapezius and in the sternocleidomastoid radiating up behind

the ear; with the ninth or glossopharyngeal, causing the distressing gripping in the throat and dysphagia; with the gasserian ganglion of the fifth, causing pain in the lower jaw; with the seventh, the sixth, the fourth, the third.

The middle cervical ganglion is connected by the gray rami communicantes with the fifth and sixth cervical nerves. It connects with the recurrent laryngeal branches of the vagus and with the deep cardiac plexus.

The inferior cervical ganglion is connected to the seventh and eighth cervical nerves by the gray rami communicantes. This ganglion, too, communicates with the recurrent laryngeal and with the deep cardiac plexus. It is frequently united with the first thoracic ganglion. Consider the sympathetic fibers in the cervical area: Pupillodilator, vasomotor to the head, secretory to the submaxillary, and accelerators to the heart are only some of them.

Further consider the connections of the gangliated cord in the thorax and lumbar regions and the great plexuses in front of them and what functions its sympathetic fibers subserve, and finally recall the close connection of the sympathetic and the emotional spheres and we understand why an explosion which begins in the upper dorsals to cause the classical angina spreads so widely and gives rise to sweats, salivation, polyuria (medullary centers), pallor, collapse, sense of impending death, so like a solar-plexus blow.

Finally the vagus: The connections of the vagus with the cardiac plexus give rise to some of the most characteristic and important symptoms. The vagus gives off branches in both the neck and chest. The cervical branches join with the cardiac nerves of the sympathetic (upper branches) and on the right side through the lower branches is distributed to the deep cardiac plexus, sending some filaments to the aorta, and on the left side sends a supply to the superficial cardiac plexus. The thoracic branches of the vagus, arising largely from the recurrent laryngeal branches, join the cardiac plexuses. The pericardial branches distribute through the esophageal and posterior pulmonary plexuses.

The vagus by these connections with the cardiac plexuses opens a pathway for most widespread stimuli, most important, of course, to the heart itself, resulting in sudden inhibition of heart-beat, a very real cause of death, according to Allbutt; to the stomach inducing its belchings of gas and motor disturbances, that so commonly afford the mistaken diagnosis of death from acute indigestion in angina cases. Diarrhea may result from irritating branches to intestines and, we are inclined to think, through its pulmonary branches or perhaps through contiguity with the respiratory center subjective sensations of insufficiency of aëration of the lung. Vomiting may be a centric stimulus or may be due to peripheral vagus irritation. Salivation and polyuria may be referred to centers in the floor of the fourth ventricle. Through the vagus supply to the esophagus, dysphagia may occur, and through laryngeal branches, hoarseness and aphonia.

We have gone into the anatomy of the nervous pathways at this length to bring home more emphatically the realization of this seismic disturbance which finds its focus about the classic anginal centers, but records its occurrence throughout the body that harbors it, and just as a seismograph may "pick up" at a distance a shifting of the crust unrecorded at its focus, so symptoms at a distance may be the expressions of disturbance of the cardiac plexuses unrecorded in the upper dorsals and lower cervicals. The most common of these remote disturbances in the gastric area (belching of gas, epigastric distress, epigastric pain, even nausea and vomiting) invite to the easy diagnosis of indigestion and how hard it is to learn that after middle-life gastric symptoms should lead our attention away from the stomach rather than toward it and, further, to remember that the thunderbolts fall from above.

Stimulation of the spinal centers cited may induce other reactions than pain. Mackenzie firmly believes that the crushing, gripping, clutching oppression about the sternum is a motor phenomenon, due to spasm of the intercostals. Excitation of the sensory branches expresses itself, too, in other terms than pain; for example, in hyperesthesia of the skin and sensitiveness to

pressure of the subcutaneous tissues and muscles; and, moreover, these stigmata last long after the pain has disappeared or may occur without pain and be present over long periods of time. We lay no small store on these findings of skin sensitive to the dragging of a pin-point, of subcutaneous tissues sensitive to gentle pinching, of breast tissues sensitive to pressure, and of sensitiveness of the muscles of the chest, neck, and arm. We consider these findings as evidences of a smoldering fire.

TREATMENT

In the treatment of angina the first step is to determine whether the heart is the seat of disease (in the sense of pathologic change) or not. The presence or absence of cardiac disease, and the patient's age are the most important factors in determining treatment and prognosis.

Before the fourth decade in the absence of physical signs of cardiac involvement precordial pains are probably not attributable to cardiac pathology; the only exceptions to this are precordial pains accompanying or following closely upon an acute infection, such as influenza, rheumatism, scarlet fever, typhoid fever, which may mean an acute aortitis.

During the first four decades the lesions found that may be associated with angina are mitral stenosis, aortic valve disease, adherent pericardium, and the rare congenital pulmonary stenosis.

In the fifth decade we think of *syphilis*, even in the absence of physical signs or of a history of infection; in this decade, too, we meet many cases of *essential hypertension*, and cardiac disease is to be thought of, although no evidence of heart change is to be detected other than the inevitable hypertrophy. This is the decade in which menopause occurs in women and precordial pains so often occur as to have given rise to the unfortunate term "pseudo-angina pectoris." We may assume until proved to the contrary that these pains are due to a disturbed correlation of *endocrines*, affecting the sympathetic. Again, and especially in women, *exhaustion* in this decade may cause angina and lessen resistance to infection from latent foci, the toxic angina of Mackenzie.

In the fifties and sixties any precordial pains and, even more, all substernal pain should be considered as of grave import; no matter how innocent the heart and vessels may seem on examination. This does not imply that many such may not still have a considerable lease on life; but the patient has henceforth to exercise every precaution and it must be remembered that the severity of the pain is not a true measure of the seriousness of the condition. In these latter decades we have to deal with (1) the hearts of essential hypertension, which are obvious enough; (2) with luetic hearts and aortæ, which may or may not be obvious, wherefore a Wassermann reaction and a searching history should not be neglected; (3) with the myocardial changes of senescence or the so-called senile heart; and (4) with coronary artery disease.

Subjective and objective symptoms of cardiac inefficiency should be sought, response to effort studied, vital capacity determined, and an electrocardiogram obtained. This last may attest to myocardial degeneration and weakness not otherwise determined, *e. g.*, delay in conduction time or deformities in the Q. R. S. complexes express damage to the conduction fibers of the bridge of His or its branches and their ramifications of Purkinje fibers, while flattening or inversion of the T wave betokens serious trouble in the myocardium while it determines far more accurately than any other method the nature and, hence, the significance of any irregularities.

Whatever the cause of the precordial or substernal pains, after the preliminary examinations the patient should be made to *rest*, for here safety lies. Further examinations and observations should be made, with minimum danger to the patient. The effect of rest on pain has both diagnostic and prognostic value. In the less serious forms of angina, toxic angina, exhaustion angina, etc., a nagging pain is likely to continue for a considerable time after rest has been established; but in the more serious type of angina, in which the attack is precipitated by effort, pain does not occur during rest, *unless* the condition is very grave. Patients, then, in whom cardiac disease is evident, or who are past middle life, and who still suffer attacks while

at rest and even in sleep, are in a dangerous plight. Prolonged retrosternal pain, with or without radiation, and severe in character should make us think of coronary thrombosis, and the only exception to rest in bed is in elderly people; in them both mental and physical deterioration may rapidly ensue and in men prostatic troubles are likely to develop; therefore, if recumbency can be avoided and even relative comfort obtained with a little activity, we should be content. It may be objected that in many of the minor forms of angina, *e. g.*, in the toxic type, one cannot make the patient bedridden permanently, and the objection is well taken, but we believe all classes should have a period of four to six weeks' rest, as all will benefit by it.

What do we mean by rest? By rest is meant a condition approximating basal metabolism so that the heart is relieved of every effort that can be eliminated. This means rest of the mind, rest of the gastro-intestinal, genito-urinary, respiratory, nervous, and muscular systems. If rest is necessary, it must be absolute to be worthwhile. The patient must stay in bed. For those who find the use of the bed-pan a trial, a bedside commode may be substituted, but walking must be interdicted.

Allbutt has suggested that this rest cure be established as in a sanitarium for tuberculosis; that is, by recumbency in the open air. We think this is a very valuable suggestion and believe that in the cases of toxic and exhaustion angina the ultraviolet rays of the sun (which are excluded by window-glass) may be of real therapeutic value.

Rest of mind is quite as important as rest of body, and usually more difficult to obtain; not only does worry over the condition obtain, but interruption of business and the *res angusta domi* it entails, keep up a mental stress that is reflected upon the sympathetic. Great tact is often required to give a proper reassurance, while still insisting on the necessity for rest, to make solicitous members of the family shake off the appearance of concern before the patient; to keep out tiresome visitors while admitting those who react happily on the patient; to exclude all business matters, unless that exclusion aggravates the situation, and then to compromise as discreetly as possible.

It is our custom to order bromids in gr. xv doses three times a day during the first week to induce a certain degree of mental quiescence and then to replace the bromids gradually with luminal in gr. ss doses three times a day and later twice a day. There is convincing evidence that many of the severe attacks of angina occurring when the patient is at rest originate in the brain, and the relief ensuing in many cases on severing the nervous pathway between the brain and the heart is quite dramatic. We shall touch upon this later; but the point we wish to emphasize here is the necessity for splinting the emotional sphere. Insomnia must be considered seriously. It is the potent factor in precipitating exhaustion and exaggerates all the legitimate causes for worry or introduces them without cause. The patient *must* be *made* to sleep.

The use of bromids as advised may prepare the way to sleep or a further dose of gr. xxx may be necessary, or one may give, just as the patient is settling down for the night, luminal gr. j to iss. This drug, in our experience, acts promptly, but if taken too long before getting ready to sleep may not be so efficacious.

It is fortunate that we possess such a variety of hypnotics, as individuals respond quite differently to one and another.

Among the milder hypnotics a favorite of ours over many years is trional. The dose is gr. xv some two hours before the hour for sleep and, failing to effect its purpose in this dose, it may be repeated after an hour or two of wakefulness. The effect will often carry over to the next night. We have found much smaller doses sufficient in many cases, *e. g.*, gr. v. Sometimes gr. ij doses every two hours through the day act happily. It may be administered in capsules, in powders, washed down, or suspended in a warm drink or dissolved in an alcoholic menstruum.

Another mild hypnotic is adalin, which contains bromid (bromdiethylacetylcarbamid). This is given in gr. v doses, but gr. x or xv may be required. It may be given as a tablet or in solution in alcohol.

Chloramid is another mild hypnotic that seems to have

gone out of fashion. It is given in powders or capsules or in whisky in gr. xv to xxx doses a couple of hours before time for sleep and, like trional, may be repeated. It may not be given in hot menstrua, as it decomposes into its constituents, formamid and chloral. In spite of its chloral content, it is said to be far less depressing and not to form "knock-out drops" when given in whisky.

More potent and compelling are the barbituric acid compounds, veronal (diethylbarbituric acid), and the monosodium salt of the same, called, in the trade, medinal. Several decidedly disagreeable after-effects of this toxic substance have led us to quite eschew it; though it has extensive use. The dose is gr. v. Medinal seems less toxic and it is soluble. It may be administered by mouth, gr. v to x; by rectum, gr. v to viiss, and subcutaneously, gr. viiss in ℥lxxv of water, which may be sterilized by boiling. We have never used it in this manner.

If sleep does not follow on the use of the milder hypnotics, one should have recourse at first to morphin or chloral. Frequent and severe attacks occurring in the night indicate the use of morphin, always hypodermically, in doses of gr. $\frac{1}{8}$ to $\frac{1}{4}$.

In high blood-pressure cases chloral hydrate is excellent. The dose is gr. x to xv at bedtime; give it in water well diluted; repeat in three to four hours if needed. Never give it in alcohol, with which it combines as an alcoholate, the highly dangerous "knock-out drop." In hypertensive cases chloral hydrate may be given in gr. v doses at four-hour intervals during the day. It was so administered during the last generation, both for its hypnotic effects and its dilating action on the vessels.

Death is believed, in some instances, to be due to vagus inhibition of the heart. Some authorities believe this to be the common mode of death. We have witnessed a sudden death in which the pulse had ceased with the onset of the attack. Allbutt is so impressed with this mode of death that he pleads strongly for the prophylactic use of atropin. This should be given in doses just short of eliciting its disagreeable effects, *e. g.*, gr. 1/150 four times a day. If the mouth is dry, vision blurred, or skin flushed, cut the dose to gr. 1/200 or less. If

well borne, remember tolerance may be established and the doses should be systematically increased. In our experience with atropin we have found that it not uncommonly seems to decidedly diminish the pain and the frequency of the attacks.

Many drugs have been advocated to relieve pain. We mention only those that we have found to be of some value. Adrenal nucleoprotein in 25 per cent. tablets of one grain each, taken four times daily, or on the occasion of pain, relieves the minor, nagging type of angina in many patients. Benzyl benzoate (20 per cent.) given in doses of ℥j to ℥ss in water ℥ij, or in cream, is effective in some cases. It may be repeated at four-hour intervals if it does not cause a distressing polyuria or gastric distress. Quinin and quinidin have come to play a considerable rôle in the cardiopathies of late. In angina accompanied by a sudden rise of blood-pressure, Wenckebach advises quinin in ½ gram (0.5) into the vein. Other Continentals advise its oral administration, asserting that it has a depressing effect on both the vagus and the accelerators, and lessens pain. We use it as the hydrobromid of quinin gr. ij often combined with luminal, gr. ¼, after each meal. It is especially useful in the nagging form of angina.

Theobromin gr. v taken three times a day after meals is quite widely commended. It is assumed to dilate the coronaries.

The salicylates are used on the theory that angina is an aortalgia. Arsenic is recommended by the older clinicians. Oxygen inhaled two or three times a day has been advocated.

Worthy of more consideration than these briefly mentioned drugs are chloral, the nitrites, and the iodids.

There are many things to recommend chloral; its relaxing effect on the contracted vessels; its sedative and hypnotic effects and, finally, the reiterated convictions of able clinicians. Mackenzie uses it in prolonged attacks and thinks it operates to prevent recurrences; he prefers to give it at night.

The nitrites may be used in hypertensive cases to lower blood-pressure and as a prophylactic against the attacks, lessening their frequency and severity. Personally, we use the nitrites in hypertension only on the occasion of a hypertensive crisis,

when the pressure has shot up beyond its accustomed level and throws an unwonted task upon the heart. Nitrites commonly do not affect the pressure at all or if they do lower it appreciably below its usual level, the patient feels the worse for it. Moreover, anginal attacks seem to occur without relation to pressure conditions.

Nitroglycerin is short-lived in its effects and if used over a period of time has to be given at very frequent intervals. Sodium nitrite operates over a longer period and may be given at two- to three-hour intervals in doses of gr. j to ij. Erythrol tetranitrate continues its action still longer and is given at four-hour intervals in doses of gr. $\frac{1}{4}$ to j.

The use of potassium iodid in syphilitic cases is obvious and we suspect that much of its ancient reputation in angina was due to its specific effect on unsuspected syphilitic aortitis; nevertheless, there are those who still believe that potassium iodid exerts an ameliorating effect on anginal pains, using it in doses of gr. x to xv three times a day, and, in some cases, increasing to the limit of tolerance.

High-frequency current has been advocated. We have not used it in angina, but have in essential hypertension: The results have elicited no enthusiasm on our part. Stevens condemns it.

We come now to more radical measures. Attempts have been made to block the pathways of pain by anesthetization of nerves and by surgical treatment. Reports have been made of anesthetization of the second and third dorsals on the affected side with cessation of pain. This, of course, is of temporary duration; resection of these nerves has been discussed, but we do not recall specific instances. Not infrequently of late we have heard suggestions to divide the pathways of pain by surgical procedure. In 1920 Jonnesco reported a case in the Bull. de l'Acad. de Med., Par., 84, 93, October, in which he established a cure by resection of the left cervical sympathetic. Jonnesco, like Allbutt, believes anginal pain to be due to irritation of the cardio-aortic plexus resulting from chronic aortitis, and Frank had, in 1899, stated that the route of the sensory fibers originating in the aorta was by way of the cervicothoracic

sympathetic to the medulla and brain by three paths: (1) The paravertebral chain, (2) the vertebral nerve, (3) communicating dorsal branches of the first thoracic ganglion. Stimuli are transmitted to and from the brain to the plexus and also between this plexus and others in the thorax and abdomen. It was believed that sudden death in angina was due to spasm of the arteries in the medulla, starting in aortic irritation. Logically, then, resection of the lower cervical and first thoracic should cut off all impulse between brain and medulla and aorta. A paper by Walter B. Coffey and Philip King Brown of San Francisco, from which we freely quote, appeared in the Archives of Internal Medicine in February, 1923. They, while appreciating the teaching of most physiologists that the sensory fibers for the heart run through the upper thoracic nerves to the stellate ganglion, originating in the spinal ganglia and passing without interruption through the sympathetic ganglia to the heart and vessels, and further realizing that there is an agreement among many physiologists that the cervical sympathetic ganglia have no connection with the brain and cord except through the sympathetic trunk and gray rami of the thoracic nerves, which connect with the cervical sympathetic through the lower cervical and first thoracic ganglia, nevertheless, because in one patient the attacks seemed to be initiated in the brain, cut the superior cardiac nerve and the main trunk of the sympathetic below the superior cervical ganglion, with complete relief. They followed this procedure in 4 cases with like results. All the cases were exceedingly severe, the attacks so frequent that any measure with even remote promise of relief was justifiable. Two of the cases were luetic.

These measures should be used only as a last resort after all other efforts have failed to relieve the pain, because the pain is a danger signal warning us that the heart is exhausted. If the pathway for the perception of pain is destroyed, what will be our guide for future activity?

If the heart is decompensated it certainly needs digitalis as any other decompensated heart and if we accept Mackenzie's theory of cardiac exhaustion as a working basis, even if there

are no physical signs of cardiac disease or decompensation and no other subjective symptoms than pain, it seems wise to administer digitalis in tonic doses. It is our custom to put all these patients on digitalis gr. iss to ij a day and more, with the usual evidences of decompensation.

Allbutt expresses his fear of digitalis, because of its stimulating effect on the vagus and does not like to use it except in combination with atropin to cut the vagus in some measure.

Furthermore, there is a long-standing tradition among clinicians that digitalis does, at least in some instances, aggravate the angina pectoris, the theory being that a greater demand is made on the myocardium through narrowing of the coronaries or a greater pressure is brought to bear on a highly sensitive aorta. Then, too, it has been noted the pain is prone to disappear with decompensation. Personally, we have felt that, in some cases under our observation, the use of digitalis has aggravated the condition, but that in the majority of cases it did not. One must watch the effect in individual instances.

Diet.—What the diet shall be depends on the individual case. We must remember that our effort is being directed at cardiac rest and that the processes of digestion increase the work of the heart. We should remember that the animal proteins take four to six hours to digest, while the carbohydrates take one to two, and order the diet accordingly. Meals should always be small in bulk and the ingestion of large quantities of fluids should be forbidden. If we are dealing with a frank decompensation, either in hearts with mitral lesions and generalized effusions, or in severe cases of essential hypertension, a Karrel diet of 800 c.c. of milk, divided into four portions, and no more fluid than insistent thirst makes necessary, is indicated. Stevens says that sometimes the Karrel diet is more effectual if preceded by blood-letting.

In cases of nephritis or essential hypertension with renal decompensation, the character and quantity of the diet are determined by a study of renal function and of retention in the blood.

In cases of exhaustion and toxic angina, insufficient diet

may have played a considerable rôle in causing the angina, and more easily digested food is needed.

In general one may say that the meals should be small, consist of easily digested food, and that meat and salt should be taken sparingly, that condiments of all kinds, pepper, paprika, mustard, horseradish, catsups, etc., should be excluded; also hot-breads, fried foods, rich pastry, highly seasoned foods, rich sauces, and gravies. The evening meal should be light. Of course, alcohol, tobacco, tea, and coffee should be interdicted, as substances increasing the irritability of the heart and interfering with its regulatory mechanism.

The diet just detailed is suitable for the lighter cases in bed and for ambulatory cases; the latter, however, should rest for a time before and after meals and avoid mental excitement (witness the deaths among elderly after-dinner speakers). Many angina patients suffer much from flatulency, eructations of gas, bloating, indigestion, and even hiccough, nausea, and vomiting. Any diet must be regulated to meet these conditions when they obtain; excessive carbohydrates and fats are especially to be suspected and such articles as have been excluded in the above list. In those with gastro-intestinal symptoms high colon irrigations are beneficial. Ordinary tap-water may be used for cleansing and to the last gallon may be added 20 per cent. ichthyol ℥j. The water must be introduced into the rectum slowly to avoid cramps, as an irritation may be set up that will reflexly initiate an attack of angina.

Prompt attention to any gastro-intestinal disturbance may abort an attack or lessen their frequency. The bowels should have careful attention and the cathartic habit avoided by the use of laxative foods, mineral oil, bran, etc., and a regular habit.

Confinement to the bed continues for eight to ten weeks except in the cases of toxic angina or exhaustion angina or those of endocrine origin or those occurring in youth. If pains persist after four to six weeks these cases may be allowed up to resume their duties in such measure as a study of the individual case seems to warrant.

In terminating the bed rest we proceed exactly as in the

case of a decompensated heart. The patient is allowed to sit up in bed for fifteen minutes the first day and the time is gradually increased until we get a gauge of his cardiac reserve. He is then allowed to sit up in a chair by the bedside for increasing periods, then allowed to walk more and more each day as his reaction to effort justifies. He is encouraged first to walk only on a level and always to avoid walking against the wind. He should always avoid haste. Inevitably in the process of increasing the freedom allowed we shall overreach the patient's reserve and discomfort will return. We must then order a régime well within the limits which we have discovered. Many patients are able to indulge in considerable exercise, such as golf and horseback riding, without provoking an attack. But we must be guided in our advice not only by the presence or absence of pain, but also by the state of the myocardium. Other patients can walk but a short distance without pain. They derive benefit by gentle massage and passive movements, but resistance exercises should be avoided. Massage may be given during the period of bed rest.

The instructions for those who return to business are not only to gauge their efforts by the distress induced, but to observe limitations designed to avoid a recurrence of the attacks; that means to shorten business hours by going later to business in the morning and returning home earlier in the afternoon; it means cultivating the week-end habit, frequent short interruptions of the business year and one or two long vacations; it means taking on no new and unfamiliar problems, the source of worry and anxiety; it means, of course, no unwonted physical effort or haste, no hurrying for cars and ferries, and, most of all, no mental excitement, such as arguments, altercations, anger, and public speaking for those unaccustomed to it. At home the patient should rest after meals and get to bed early.

The Attack.—When the attack is provoked by exercise and is not too severe in character, immediate cessation of effort is followed by relief; when, however, the attack is severe, coming on with or without effort, medication is imperative to gain relief.

When Lauder Brunton introduced the use of nitrites in this condition, it is no exaggeration to say he conferred a boon upon humanity. Their use is universal and no physician is so ignorant as to omit them. The amyl nitrite pearl containing 3 to 5 minims is commonly used, but we use more and more the nitroglycerin tablet in its stead. The effect of amyl nitrite is immediate, but the crushing of the pearl in the midst of an anginal throe is sometimes difficult and the flushing and throbbing of the face disagreeable, though, of course, of little significance compared with the relief afforded. Nitroglycerin, when used, is commonly given under the skin or by the mouth; but the effect is not nearly as prompt as when placed under the tongue and absorbed there. Not infrequently, when so administered, the promptness rivals the amyl nitrite and causes a like flushing and throbbing, but rarely so severe. The dose is gr. 1/100, 1/50, 1/25, or 1/10. We do not know a toxic dose; but one unnecessarily large will magnify the discomfort.

Lauder Brunton believed that this remarkable effect of nitrites in angina was due to lowering blood-pressure through dilatation of the vessels, but it has been demonstrated innumerable times that just as prompt relief comes without any lowering of the blood-pressure at all, and even in cases in which the blood-pressure has been increased in some measure. It must, then, have some anodyne action. The attack itself may, or may not, cause an increase in blood-pressure; in some instances it induces a fall.

We are accustomed in ordering nitroglycerin to be taken under the tongue to prescribe for hypodermic tablets as probably being fresher and more soluble. Spirits of glonoin ♏j, ij, iij, or even x on the tongue is ideal, but it is almost impossible to keep the highly volatile substance from escaping from the containers, causing a disagreeable odor and sometimes physiologic effects.

The objection to swallowing the dose to secure absorption is that it entails possible loss in potency by the action of the gastric secretions and in the act of swallowing vagus excitation follows, which it is desirable to avoid, as vagus excitation is

believed to be responsible, as we have explained, for sudden cessation of the heart-beat in some cases.

If, as in some instances, the nitrites do not relieve the pain, or it quickly recurs, *morphin* is indicated. It must be given hypodermically and the dose large, gr. $\frac{1}{4}$ to $\frac{1}{3}$, and half as much again in fifteen minutes, if the pain is not abated. There is an extraordinary tolerance for morphin in these attacks and the dose is not to be gauged by ordinary rules but by results.

If morphin is not effective, we are accustomed to use from 5 to 16 minims of trivalin (morphin-caffein-cocain-isovalerianat). This drug often gives prompt relief when a grain of morphin will fail.

We are accustomed to continue the use of morphin at regular intervals for three or four days after an attack. In this way we hope to give a maximum of rest to the heart and block the reflexes that initiate the pain. We then substitute luminal or bromids as described above. On theoretical grounds it is advisable to use atropin with the morphin to lessen the danger of cardiac inhibition through the vagus.

Chloroform.—When morphin may not be used because of an idiosyncrasy, or because it cannot be given under the skin, chloroform must be considered in the cases in which the nitrites are ineffectual. There are those who think the use of chloroform is accompanied by risk, more especially in low blood-pressure cases; on the other hand, Osler says he has never seen any dangerous results from its use. We do know that a painful operation, especially about the nose, done under a partial chloroform anesthesia has more than once resulted in death, presumably by reflex through the vagus, and this knowledge may offer some theoretical objection; but the agonizing pain cannot be disregarded and we may equally agree that the relief of pain lessens the danger of sudden death.

Perhaps the best way to administer chloroform in these cases is to allow the patient to take it himself, if he is able to do so. A sponge, moistened, may be placed in a wide-mouth bottle or tumbler on which chloroform is dropped, the patient inhaling until he becomes drowsy, when the bottle drops from

his hand, thus preventing an excess being taken. We have recently used chloroform successfully in those in whom a grain of morphin failed to give any relief from an agonizing pain. After the initial attack was relieved we were able to keep them comfortable with morphin gr. $\frac{1}{8}$ every four hours.

Ether has been used, but is less prompt and efficacious.

Circulatory collapse may follow upon a severe attack, when stimulation is indicated. In urgent cases, strophanthin in $\frac{1}{2}$ mg. doses into the vein or muscle is used, and in less urgent ones digitalis in gr. iij to vj doses into vein or muscle, and in high blood-pressure cases with pulmonary edema, digitalis in combination with nitroglycerin is used. The rapid relief of pulmonary edema in the hypertensive cases following upon nitroglycerin is at times instantaneous and most dramatic.

In low blood-pressure cases adrenalin is indicated ♏x to xv into muscles, ♏ij to iv into vein. Beside increasing blood-pressure it dilates the coronary vessels, which is of theoretical significance.

Less valuable is an intramuscular or intravenous injection of a double salt of caffein and sodium benzoate or salicylate gr. v to viiss. As the hypodermic injection of this drug so frequently gives severe local reaction we give it in the same dosage by mouth with equally satisfactory results.

Less effective measures which one may also try, especially in cases with epigastric discomfort and gas, are inhalations of ammonia or aromatic spirits of ammonia; a glass of hot water containing: (1) Sodium bicarbonate ℥j alone or with spirits of peppermint gtt v to x, or (2) whisky ℥j to iv, or (3) such carminatives as Hoffman's anodyne or compound spirits of lavender ℥j. Heat may also be applied to the surface of the body in the shape of fomentations or mustard paste or other counterirritant. Some observers advise cold compresses or packs; we have never used them. The very multiplicity of the measures used is a commentary on their value.

Now let us consider some of the by-paths that lead from this relatively smooth highway.

1. One of them leads to a peculiarly *stubborn* attack, which

sets at defiance our miracle-working nitrites: It is very severe, felt under the sternum or over the precordium and now and then in the epigastrium or in the right or left hypochondrium; and then we may not think of the heart at all, but conjure up pictures of a perforated gastric ulcer or gall-bladder attack or acute pancreatitis. Not only is the attack severe, but it persists or repeats itself. Such attacks should always make us think of *coronary thrombosis.*

With the onset of the attack the evidence of shock is striking; there is cyanosis or a blanched, leaden hue of the skin, a peculiar pinched appearance to the nose, an agonizing breathlessness that seems purely subjective for the respirations do not change in character, but the patient complains bitterly that he can get no air; a small, thready or irregular pulse; faint heart-sounds, sometimes a pericardial friction rub; a fall in blood-pressure; râles at both bases or a frank pulmonary edema; a failure of the right heart may back the blood onto the liver, which becomes enlarged and tender. There is a fear of death, though death is less likely to occur during the attack than a week or two later. Fever is an accompaniment and may rise to 101° or 102° F. Moreover, there is a leukocytosis at times, usually slight, but it may be pronounced, 20,000 to 30,000. Friction rubs, leukocytosis, and fever might make one think the infarct was in the overlying lung; sometimes the scleræ are icteric.

Several observers have attempted to correlate certain electrocardiographic changes with thrombosis of the coronaries, *e. g.*, Pardee says, "The characteristic changes appearing a day or two after the obstruction are as follows: the Q. R. S. group is usually notched in at least two leads and usually shows left ventricular predominance. The T-wave does not start from the zero level of the record in either Lead I or Lead III, though, perhaps, from a level not far removed from it, and in this lead quickly turns away from its starting point in a sharp curve, without the short, straight stretch which is so evident in normal records preceding the peak of the T-wave. The T-wave is usually of larger size than customary and accordingly shows a

somewhat sharper peak. The T-wave is usually turned downward in Lead II and in one other lead." He thinks well over two-thirds of the cases show what may be considered electrocardiographic evidence of infarction due to stoppage of the coronary (Arch. Int. Med., vol. 26, 1920, p. 244).

Smith says that in occlusion of the left coronary the T-wave is reversed in Lead I alone or with II or with II and III. It is sharp-peaked; the Q. R. S. complex is decreased in amplitude. He believes the T-wave deflection is dependent on the formation of an area of infarction in the apical region of the left ventricle; decrease in the Q. R. S. complex he says is associated with more extensive and disseminated changes in the myocardium. Animal experimentation seems to corroborate clinical findings. On the other hand, Longcope had 9 cases proved at autopsy to have had occluded coronaries, none of which showed conclusive cardiograms, either in T-waves or in Q. R. S. complexes.

The treatment of the attack of coronary thrombosis demands immediate action. The patient must be put in bed at absolute rest with the least possible disturbance, even avoiding taking off his clothes. Should this be the first attack of chest pain that the patient has experienced we naturally try first the effect of nitroglycerin and morphin gr. $\frac{1}{4}$ as described for angina pectoris. If these fail to relieve the pain in fifteen minutes we should give morphin gr. $\frac{1}{4}$ and atropin gr. 1/100 hypodermically, and if relief is not obtained after another half-hour we repeat the dose. In the meantime we may give nitroglycerin gr. 1/100 every fifteen minutes. If we feel certain that we are dealing with a coronary thrombosis we should give immediately morphin gr. $\frac{1}{2}$ and atropin gr. 1/100 hypodermically and repeat gr. $\frac{1}{4}$ of the morphin if not relieved in thirty minutes. At the same time we should give nitroglycerin gr. 1/100 to 1/50 to be dissolved under the tongue.

Often more effective than the morphin is the trivalin in doses of 1 c.c. by hypodermic. This may be repeated in doses of 0.5 c.c. after thirty minutes.

When no relief is afforded by the morphin, chloroform should be tried. The patient should not be disturbed for any reason

until well under the influence of morphin and free from pain for four or five hours. Undressing should be done with the least possible exertion. The patient is then kept at absolute rest under morphin given at regular intervals for at least a week. The morphin can then be decreased gradually and bromids or luminal or chloral substituted for it. The use of sedatives is continued for four to six weeks so that the patient is content to be at absolute rest. The nurse should feed the patient, turn him in bed, etc., so that he exerts himself to a minimum extent. In the seventh week sedatives are decreased and the patient is allowed to begin turning in bed, to feed himself, etc. At the end of the eighth week he may begin sitting up in bed, and at the end of the tenth week he may begin sitting up in a chair. Further freedom is given as in the anginal cases.

In many of these cases we find that their cardiac reserve at the end of fifteen to twenty weeks is limited to sitting up a few hours a day and taking a few steps. After six to twelve months they can walk only a few blocks without substernal discomfort or breathlessness. They can never return to an active life and, at best, we can promise them only a limited freedom—henceforth they are semi-invalids.

The same régime should be followed during bed rest as we have described under angina.

2. Aside from the acute and severe attacks described, the involvement of the coronaries is believed by some authorities to add certain distinctive features to the case, *e. g.*, that it is coronary disease that induces the night attacks, after the patient has been asleep a few hours or when he is sitting quietly. It is thought that the pain is often high in the chest, under the clavicles and in the neck, a squeezing, a clutching at the throat which is rather a discomfort than pain (Robey). Robey looks on premature contractions, auricular fibrillation, and heart-block as being almost confirmatory of coronary disease. It seems to us that this is putting a terrible onus on so common a condition as premature contractions.

3. It is obvious that infection, if present, must play no mean rôle in aggravating, if not in causing, the conditions giving rise

to angina, whether we accept Mackenzie's or Allbutt's theory of coronary occlusions, consequently every focus of infection should be removed and treated; sinuses, tonsils, teeth, three notorious resorts of pyogenic infection, investigated; the gastro-intestinal canal and the genito-urinary tract inspected. We have by the Murphy maneuver over the gall-bladder excited reflex pain in the upper left intercostals, the usual site of angina, in a case of angina with a history of cholelithiasis.

Of course, of all infections, lues should be the most conscientiously considered. The laboratory has today become apotheosized and brooks no other gods on Olympus. The Wassermann reaction will be invoked if syphilis is thought of at all; but unhappily, all to often, a negative reaction will be taken as an acquittal. We must remember, then, how often the Wassermann reaction is negative in the late stages of syphilis and go into the patient's history with care; if there has been exposure, and all the more if there has been gonorrhea, the patient should be indicted and evidence sought in so-called "venereal sores or chancroids," unexplained eruptions, in miscarriages, in stigmata in children and by a detailed examination for such lasting marks as syphilis strews about the body in scars, leukoplakia, etc. Mental disturbances invite an inspection of the cord-fluid. Aneurysm spells syphilis; aortic insufficiency occurring in adult life, especially in the absence of hypertension, makes the diagnosis more than probable.

The angina of a syphilitic aortitis is severe, often agonizing. Sometimes an intense paroxysmal dyspnea occurs with syphilitic angina, most violent in character, the patient becoming blue and struggling like one who is being throttled. Such attacks should make lues probable. The angina, like other luetic pains, may occur, especially at night, and give the hint. When at all in doubt give the patient the benefit of the specific treatment. This is not the place for a dissertation on antiluetic treatment; but we will merely say that it is better to begin in any serious cardiac condition with the old mixed treatment or a course of mercury, *e. g.*, weekly doses of salicylate gr. $\frac{3}{4}$ to j for a course of 6 doses, giving the iodid of potash at the same time, before

beginning arsphenamin. Beginning the latter at once often precipitates violent reaction.

4. Last, we must consider a vast number of cases that, in a way, are the most important of all; cases in which we cannot persuade ourselves that the heart is the seat of structural pathology; cases in which we feel that the causes for the angina are remote from the heart and that if we could only discover them, a part at least might be eradicated. This includes the angina of early life, the so-called "pseudo-anginas," the toxic anginas, the exhaustion anginas, and so on.

Every careful student of the subject has recognized them and has struggled to classify them—with unsatisfactory results—and yet some kind of a grouping is necessary for a working basis. It does, indeed, seem probable to us that poisons may affect the cardiac plexuses to the induction of pain, when no lesion of the aorta or myocardium exists. We further realize that these same toxic substances may, at the same time, be effecting changes in the structures mentioned, but not so material as to be incapable of resolution or at least cessation if the toxic irritant be removed. It goes without saying that the peccant substances can seriously aggravate the lesions and the pain in an already damaged heart. We have touched upon the latter already and feel justified in considering the unproved pathologic cases under the caption of toxic angina.

The toxic substances which cause toxic angina may be chemical or bacterial. Among the former may be mentioned tobacco, coffee, alcohol.

Tobacco angina has long been insisted upon and it is fair to presume that it exists. When pain occurs in the young indulging unduly in tobacco it is probably the real cause. At any rate its discontinuance affords relief. We think it hardly worth while to discuss the arteriosclerosis once attributed to it. In people of anginal age tobacco certainly should be interdicted, for its use provokes pain in a pathologic heart the seat of angina. In the young suffering from sympathetic imbalance, often due to endocrine imbalance or in an adult in whom instability of the sympathetic system is obvious, all substances

increasing nervous irritability and cardiac irritability, such as tobacco, coffee, and alcohol, may well be suspected as initiating the anginal attacks.

Bacterial poisons are to be sought for in every nook and corner of the anatomy. It is the head that most commonly harbors latent foci of infection; the teeth, every devitalized member of which should be *x*-rayed and the physician himself should see the *x*-ray. More than that, he should remember that *x*-ray evidence of an infected tooth is that of an advanced process and that a skilful dental surgeon may detect infection before bone absorption has taken place. Next the tonsils; history of sore throats, involvement of the regional lymphatic glands, expression of infected material are all to be considered; neither are the adenoids or lingual tonsil to be forgotten. The worst offenders are incompletely removed tonsils, under whose scar tissue is locked up infections. Sinuses next; with any history relevant to their involvement, inspection, transillumination, *x*-rays should be made. It is surprising how many infections of the sinuses are to be found when no history of an acute attack can be elicited.

The next most important field is the gastro-intestinal tract. Here foci of infection may be harbored in the stomach, gall-bladder, appendix, in diverticuli, in hemorrhoids, and from these structures undoubtedly arise reflexes overflowing onto the anginal area, as well as toxins. In the genito-urinary area are to be sought infected tubes, infected prostates, infected bladders and kidneys; in the lungs, chronic infections of the bronchi, and even the skin may be the seat of an infection contributing to the distress of the cardiac plexuses.

In these cases we feel that something very real may be done for the patient by removal of foci, by recovering the infecting organisms and making use of the vaccines derived from them.

Essential hypertension affords no inconsiderable number of cases. We must direct our attention, so far as possible, to ameliorate the degree of hypertension and avoid sudden strains of physical and mental excess and to promptly meet the crises of more obscure origin. Renal function demands our considera-

tion as well. This is not the place to enlarge upon the treatment of hypertension; but we will merely add that no drug can affect it in any way comparable to rest.

Exhaustion Angina.—Another field for inquiry in cases of angina without obvious cardiac lesion are causes for exhaustion. Mackenzie makes much of this group, naturally, as his explanation of the anginal attack is exhaustion of the function of contractility, whether due to diseased myocardium, poisoned myocardium, or fatigued myocardium.

He sees among the causes overwork, worry, sleeplessness, poor (or insufficient) food, bacterial infections, diseases of other organs, excessive child-bearing, too much tobacco, alcohol, and food.

This group cannot be sharply dissociated from toxic angina, nor from the groups that follow; such divisions we have made are chiefly for the purpose of calling attention to proper fields of investigation with a view to relief.

The treatment of such cases is obvious. Removal of causes, rest under much the same régime and medication as already described.

Reflex Angina.—We know of no such division having been made and our only justification for using the term is our conviction that angina may arise from reflexes originating at a distance. Most of these reflexes start below the diaphragm; it may be the gall-bladder. We have called attention to the case in whom deep pressure over a known diseased gall-bladder caused no local pain, but one in the distribution of the upper dorsals, adjacent to the manubrium on the left side and between the scapulæ. Cardiospasm and pylorospasm can cause intense pains beginning in the epigastrium, radiating up the sternum and out into the jaws. We have known the reverse route to be taken beginning like a toothache or neuralgia of the jaws and spreading down to the epigastrium; such pains often radiate into the back between the shoulders. We have not ourselves seen a radiation into the arms.

We are firmly convinced that congenital bands and membranes and probably adhesions, too, either directly or indirectly,

cause painful reflexes into the anginal area. Whether this comes from the changes in the membranes, such as thickening and shortening causing irritation of the sympathetic fibers directly or by interfering with the functions of the stomach and intestines mechanically, or through the vagus altering motility and secretion, or encouraging stasis with putrefaction, fermentation, or infection, we do not know, but we have seen cases in which the exacerbations of the anginal pains are concomitant with disturbance of the gastro-intestinal function in proved membrane cases.

Mackenzie discusses this group under his toxic angina, and he states his belief that the most common cause of the angina is to be found in the intestinal tract. He calls attention to the fact, and we want to emphasize it, that one may find on the abdomen of these cases hyperalgesia of the skin and of the structures beneath with a sense of slight resistance. He often noted this in the right iliac region, when the patient had experienced slight pain, which readily gave rise to the mistaken diagnosis of appendicitis. In such of these cases as were operated he found a great many adhesions about the cecum. We want to quote a sentence from him: "All inquiry in which I am at present engaged reveals that adhesions here and in other parts of the intestinal tract are exceedingly common and are associated with or caused by stasis and decomposition of the intestinal contents." We believe from our own considerable number of operated cases that many of these so-called adhesions are congenital bands and membranes, and almost invariably such cases are associated with widespread sympathetic disturbance. It can readily be appreciated how nagging at the sympathetic nerves, toxins and exhaustions, perhaps endocrine disturbances and an hereditarily unstable nervous system interplay to produce the pictures and how futile it is to draw hard-and-fast classifications. Ours, we reiterate, are only to facilitate search for a cause.

These cases cannot be conscientiously treated without such a detailed search.

Endocrine Angina.—We should be loath to make such a classification at a time when all medicine is threatened with

engulfment in the capacious maw of endocrinology; but there are certain glaring examples. We cannot disregard the instances of anginal pain associated with hyperthyroidism and we cannot but feel that the precordial pains of women at menopause, not ascribable to demonstrable cardiac lesion, called pseudo-angina, must be due, in some instances, at least in some measure, to disturbed endocrines. We see boys or girls at puberty suffering from pains about the heart, and we see the same in individuals in whom we have well-recognized evidences of endocrinopathy. The younger the patient is, the more certain we are that the anginal pains are not of cardiac origin, unless, indeed, the examination discloses a cardiac lesion; even women under fifty with angina and no demonstrable cardiac disease or hypertension, probably owe their attacks to one of the causes named, operating elsewhere than in the heart.

There are sundry peculiarities about the angina in these cases. In the first place the *pain occurs* when the *patient is at rest*, even when free from excitement. It is apt to be a nagging pain. Sometimes the patient recognizes other sympathetic disturbances; he is "on edge," has gastric disturbances, a spastic constipation, a feeling as if he were definitely poisoned. The attacks, however, are not always light; they may be of agonizing severity and widespread. They may come on with exertion, but at any time they may *fail to appear after considerable exertion.*

Another *noticeable* feature of these cases is the *marked* and extensive *hyperesthesias* and *hyperalgesias*. These are *not striking in the serious anginas*. So marked are these hyperesthesias at times that the warmth of the hand over the area affected is like that on a skin burned by mustard—the underlying subcutaneous tissues and muscles share in the hypersensitiveness. Moreover, these areas are widespread, occurring now on the abdomen, now on one or both thighs; one patient thought a pin was in his pajamas scratching the thigh, and sought long and vainly for the offending object, and though no mark or redness could be seen, was hardly persuaded until both thighs were affected simultaneously.

In women near the menopause, or who are much fatigued,

or lose much sleep, there is a characteristic ache just under the left nipple, with a very sensitive intercostal at this point. The left breast and often both are hyperalgesic. The manner in which these areas dodge from left to right, from chest to abdomen, and the frequency with which the pains reflect into the right arm as well as left are quite unlike the serious cardiac cases.

These cases show other sympathetic dysfunctions, such as palpitation, premature systoles, breathlessness, weakness, and much exhaustion on little effort. There is a tendency to fainting, on standing, or in hot, confined places; this we see in children with endocrine imbalance at puberty. There are further evidences of sympathetic disturbance—cold, cyanotic hands and feet, numb fingers, red nose, chilliness even in warm weather, leading to heaping on bedclothes in a summer's night.

The treatment of endocrine anginas demands the correction of any organic pelvic condition, treatment of hyperthyroidism, and of the menopause syndrome in the usual way.

Hydrobromid of quinin gr. ij and luminal gr. $\frac{1}{4}$ after meals often afford relief from symptoms.

Any treatment instituted must be accompanied by several weeks' rest in bed as described above.

CLINIC OF DR. BENJAMIN H. ARCHER

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CLINICAL ASPECTS OF CHRONIC ARTHRITIS

ALMOST every contribution to the literature of chronic arthritis is prefaced by a consideration of its classification. In fact, it has been said that every investigator of this disease has his own terminology. This may at first glance impress one as a purely academic question, of no special significance in the management of a rheumatic case. However, from a clinical point of view, the classification one uses is of extreme importance. As a rule, the entire treatment of the arthritic patient depends upon the category into which he or she is placed.

Virchow[1] originally called all cases of chronic joint disease "arthritis deformans," but this term was found to be too inclusive. Garrod[2] was the first to separate arthritis into two main divisions. The first he called rheumatoid arthritis, and the second, osteo-arthritis. The English writers still use this classification. Goldthwait[3] of Boston applied the terms "atrophic" and "hypertrophic" to the same groups. Nichols and Richardson,[4] working along strictly pathologic lines, spoke of the two types as proliferative and degenerative arthritis. Ely[5] simplified the matter and called them the first and second great groups. Cecil and Archer[6] are beginning to think in terms of "infectious" and "non-infectious" arthritis, associated respectively with inflammatory and degenerative pathology. We feel that the rheumatoid arthritis of Garrod, the atrophic arthritis of Goldthwait, the proliferative arthritis of Nichols and Richardson are different terms which describe the same pathologic entity and probably represent an infectious process. On the other hand, our experience is forcing us to the conclusion that the second group,

variously called osteo-arthritis, hypertrophic arthritis, and degenerative arthritis, is probably the result of a non-infectious process and is due to senile changes comparable in their pathology to the degenerative lesions of arteriosclerosis and chronic interstitial nephritis.

It thus becomes apparent that the classification of arthritis is of real clinical significance. On the one hand, we are treating a chronic infectious process, and on the other hand, we are dealing with a condition in which foci of infection play no important rôle. We are firmly of the belief that the scepticism which is felt by many concerning the removal of foci of infection in arthritis, is in no small measure due to a failure to differentiate the infectious from the non-infectious type of the disease. It is this phase of the problem of arthritis which I wish to consider, as it has a direct practical bearing on every case of joint-disease that I am called upon to treat.

In the last report of our series of cases Cecil and I adopted the pathologic terms "proliferative" and "degenerative" to describe the two main divisions of chronic arthritis. In this we followed the classification of Nichols and Richardson who thus described the two types of this disease in their classic monograph on the pathology of the arthritides. These latter writers divide the joint lesions of chronic arthritis into two very definite pathologic groups: (1) Those in which the primary change is an inflammatory reaction of the synovial membrane. (2) Those which arise primarily as a degeneration of the joint cartilage. The first they designated as proliferative, and the second as degenerative arthritis. These two pathologic types are characterized by distinct gross and histologic differences and each type manifests itself clinically by a characteristic group of symptoms and signs.

In proliferative arthritis, proliferation of the synovial membrane produces a layer of granulation tissue which sooner or later may extend over the joint cartilage with more or less destruction of the cartilaginous tissue. Furthermore, proliferation of the perichondrium may lead to the formation of new cartilage or bone. The capsule and other periarticular structures

are also involved in this process. These truly inflammatory changes, if not checked, lead eventually to partial or complete destruction of the joint cavity with subsequent fibrous or bony ankylosis. In the opinion of Nichols and Richardson, these changes represent a reaction to injury that may be either bacterial or toxic in its nature.

In degenerative arthritis, the primary change in the joint is a degeneration of the cartilage of the articular surfaces, which gradually becomes softened and eroded. The underlying bone thus becomes exposed, so that eventually two bony surfaces may be in contact. As a result, the exposed bone becomes extremely dense and acquires a high degree of polish. The head of the bone is enlarged and leads to an actual increase in the size of the articular surface. Secondary changes consist of an increase in the activity of the perichondrium at the periphery of the joint where the cartilage and capsule come together. As a result of this perichondrial activity, there is a new formation of cartilage which may be transformed into bone. This newly formed bony tissue takes the form of lipping and irregular exostoses, so readily demonstrable in roentgenograms.

This important work of Nichols and Richardson corroborated the earlier work of English and German pathologists and has more recently been verified by the studies of Ely. According to these authors, these two types of chronic arthritis could not be distinguished etiologically. They thought that the same cause might produce the primary change either in the synovial membrane or in the cartilage, and that different causes might produce the same type of pathologic lesion.

About two years ago we classified 612 cases of chronic arthritis,[6] which had come under our observation at the Cornell Clinic. Of this number 414 were of the proliferative, and 182 of the degenerative type; 4 cases of gout, 2 cases of intermittent hydrops, and 10 unclassified cases completed the series. It is convenient clinically to subdivide these main divisions into subgroups. Under proliferative arthritis we recognize three such groups: (1) Chronic infectious arthritis referable to foci of infection; (2) the specific arthritides that include all those cases

whose causative organism is known, such as the gonococcal, tuberculous, and syphilitic forms of arthritis, and also the surgical joints due to infection with the staphylococcus, pneumococcus, meningococcus, etc.; and (3) the true arthritis deformans, which, at the time of our report, we considered a chronic progressive polyarthritis of unknown origin, but today we are beginning to feel may represent a severe form of focal infectious arthritis.

The cases of degenerative arthritis also lend themselves to subgrouping and we have divided them up into the arthritis of the menopause, the degenerative monarticular arthritis, formerly called morbus coxæ senilis, and lastly, senile arthritis. All these are due to senescent changes and are probably non-infectious.

It would take us too far afield to consider separately each of the subdivisions mentioned above. It will suffice for our purpose to describe the outstanding groups in each of the two main divisions and by drawing a parallelism between them show that pathologically, clinically, and probably etiologically we are dealing with two wholly different types of the same disease.

In the study mentioned above, chronic infectious arthritis furnished 379 of the 414 cases of proliferative arthritis. The arthritis of the menopause supplied 145 of 182 cases of degenerative arthritis. Our own experience makes us feel that these are the most common forms of each type and we are convinced that the former is infectious and the latter non-infectious in origin.

We recently analyzed 200 of our cases of chronic infectious arthritis.[7] To summarize the essential features of this disease we may say that this type of arthritis occurs much more frequently in females than in males. It is essentially a disease of young people, the average age being thirty-five. Exposure plays a secondary rôle. The most common etiologic factor is some primary focus of infection. In our series infected tonsils were the most common focus, occurring either alone, or in combination with other foci, in 61 per cent. of the cases. Next in frequency were infections about the teeth. The teeth alone, or in combination with other foci, were the source of infection in

33 per cent. of the cases. The sinuses, prostate, gall-bladder, colon, and cervix harbored foci of infection in a few cases. It is interesting to note that the age-incidence was much earlier in the tonsil cases than in the dental cases; the average age being thirty years in the former, and forty-two years in the latter group. The patient often dates the onset of symptoms from some disturbance of the physical equilibrium, such as an acute infection, exposure to cold, a surgical operation, or a confinement. A majority, but not all of the tonsil cases give a history of a preceding attack of tonsillitis or sore throat. Chronic infectious arthritis is a polyarticular disease which may involve any joint in the body. It may come on suddenly with fever and other acute symptoms simulating acute rheumatic fever, or the onset may be gradual. Locally the lesions are characterized by inflammatory and periarticular changes in the joints involved. It is almost always migratory in its early stages, but after several attacks the joints become permanently injured. The fingers, knees, and shoulders are the joints most frequently affected. This is a painful form of arthritis, particularly in the early stages when there is apt to be considerable periarticular involvement. Physical examination usually, but not always, reveals a patient somewhat underweight and anemic. The joints affected, as a rule, present a characteristic appearance. There is some swelling of the soft parts and the overlying skin is warm and sometimes reddened. The swelling is due for the most part to the outpouring of an inflammatory exudate into the periarticular structures. Tenderness is usually present and motion, either active or passive, is usually painful. In the later stages the swelling may disappear, but usually there is enough new growth of fibrous tissue about the joints to cause a persistent periarticular thickening. This is shown most typically in the finger-joints in which the characteristic fusiform enlargement may be present for years. Ankylosis is quite common in this form of arthritis, but usually does not occur until the second or third year of the infection. It is at first fibrous, but later may become bony.

In contrast with this description it may be of interest to give

a brief clinical résumé of the arthritis of the menopause. Next to infectious arthritis this has been the most common type of arthritis that we have encountered. More than 25 per cent. of our whole series fall into this group. As previously reported, arthritis of the menopause is a chronic degenerative polyarthritis occurring in obese, middle-aged women, at or just after the menopause. In a series of 50 cases, reported three years ago, the average age was fifty-two and a half years. In almost every case the patient was considerably overweight. Symptoms usually appear during the first two years after the menopause. Sometimes the arthritis occurs simultaneously with the menopause, and in 15 of a series of 200 cases, tabulated one year ago, the disease appeared shortly after a premature menopause due to panhysterectomy or oöphorectomy. At times the rheumatic symptoms have preceded the change of life by a short interval. Foci of infection are rarely demonstrable and for this reason we question very seriously the infectious origin of the disease. The morbid changes are those of a degenerative arthritis. The cartilage becomes thin and there is lipping and spur formation at the margin of the joints involved. The joints most frequently involved are the knees. The lumbar vertebræ and the bones of the feet are often affected. In a large percentage of the patients there are well-developed Heberden's nodes on the distal phalangeal joints.

To summarize the salient features of both types in parallel form: The average age at onset of chronic infectious arthritis is in the third and fourth decades; menopause arthritis in the fifth and sixth decades. The weight in the former is normal or below par. In the latter obesity is common. The hemoglobin in the former is low; in the latter is normal. In chronic infectious arthritis foci of infection are usually present. In menopause arthritis they are usually absent. The pathology of the first type consists of proliferative changes; in the second type of degenerative changes. Chronic infectious arthritis is apt to be migratory; the menopause type is a localized process. *x*-Ray of the former shows narrowing of the joint space; in the latter lipping and exostoses are present. The special sign of infectious

arthritis is the fusiform finger-joint. The special sign of menopause arthritis is the finding of Heberden's nodes associated with grating knee-joints.

These two groups of arthritis differ so remarkably in every respect that it is unreasonable to suppose that they are due to the same etiologic factor, *i. e.*, foci of infection. As far as we have been able to determine the matter clinically, particularly by the use of the therapeutic test, foci of infection have nothing to do with menopause arthritis. At least their removal has never improved or cured a single case in our entire series. The claim of Burbank and Hadjopoulos[9] that the degenerative type of lesion which is present in menopause arthritis, is due to a Streptococcus viridans infection is interesting, but absolutely without any proof. In fact, all the evidence at hand points strongly to a non-infectious causation.

Llewellyn,[10] discussing climacteric arthritis before the Royal Society of Medicine, gave the following reasons in support of the contention that a deficiency or perversion of the thyroid and ovarian hormones is responsible for this variety of osteo-arthritis.

"I have met with this clinical syndrome not only during the normal climacteric, but also when an artificial menopause has been induced by an oöphorectomy.

"Again, in a case of acute Graves' disease under my care, the thyroid swelling underwent recession through functional exhaustion of the gland and arthritis followed."

Burt, speaking at the same symposium, gives the details of an interesting case which illustrates the same causal relationship:

The patient was a girl, fifteen years of age, who complained of swelling in both knees. Menstruation began at the age of fourteen. At the age of fifteen, following a severe shock, the periods stopped and the arthritis came on. On examination the knees were found to be puffy and swollen and there was soft creaking present. There was some panniculitis on the inner side of the knees. The patient was remarkably overweight. Three months after the first examination, during which time the patient was given thyroid, the periods returned, but were scanty. After

the return of the menstrual function the condition of the knees completely cleared up.

Coates[12] cites the following 2 cases:

A. A girl, aged eleven, who came under his care for pain in the knees. She showed an early girdle obesity, advanced sexual characteristics, pituitary fingers, and painful knees with panniculitis.

B. A woman in the twenties, complaining of stiffness and pain in the knees with an acromegalic facies, an enlarged sella turcica (*x*-ray shown) and typical menopause arthritis.

Coates is of the belief that in cases of artificial menopause, natural menopause, and thyropituitary failure, the same findings are present; namely, obesity, general and girdle; a derangement of the sugar-storage mechanism; a lowered basal metabolic rate, and a special type of arthritis.

Cumberbatch[13] added some novel evidence to the conception of the disease as one of endocrine imbalance. Some of his cases occurred in women at about the time the menstrual function was being established. They developed arthritis when amenorrhea occurred. No evidence of a primary focus of infection could be found. The application of diathermy to the interior of the pelvis restored the menstrual function and brought the arthritis to an end. Other cases occurred in women at the time of the menopause. In many the climacteric occurred early, and was followed by arthritis. In these cases the application of diathermy usually arrested the arthritis when menstruation recurred following its application. In one case the menses recurred after an interval of ten years. In another case the interval was three and a half years.

Sawdon[14] cited another case illustrating the same principle. Deep *x*-ray therapy had been given for uterine fibroid, successfully. Twelve months after the onset of an artificial menopause, well-marked symptoms of menopause arthritis were present.

To this array of evidence as presented at the symposium on "Climacteric Arthritis," held by the Royal Society of Medicine, on February 4, 1927, we can add the following interesting data: During the past five years Cecil and the writer have encountered

4 cases of the menopause arthritis syndrome in males. In each case the creaking knees and Heberden's nodes were associated with diminished sexual power, and in one of the cases with complete impotence. The last case of this type seen occurred in a physician who recalled that the arthritis came on shortly after his loss of sexual vigor became apparent to him.

The almost unanimous opinion of the English investigators that there is a definite type of arthritis which comes on after disturbance of the menstrual function coincides completely with our own experience. The only question involved at the present time is the terminology of this type of the disease. Because of the fact that typical infectious arthritis may occur at the time of the menopause as well as at any other time of life, and for the reason that cases are on record in which thyropituitary-gonadal failure in women, and occasionally in men, is found to give the same syndrome which Cecil and I have described, it is a moot question whether or not we are justified in using the term "menopause" or "climacteric" arthritis. The British observers are more inclined to favor hypoglandular arthritis. Perhaps this describes the causative factor more accurately than the use of the term "menopause arthritis." Whatever word may finally be used to designate this clinical syndrome, there seems to be little question that sufficient evidence has been accumulated to prove that this type of the disease is in all probability endocrine in origin. At any rate, it is a non-infectious process and is not in any way related to foci of infection.

The two types of the disease I have discussed differ so markedly that, as a rule, a differential diagnosis can readily be made. After this is done the treatment follows naturally. In the infectious group too much emphasis cannot be placed on a relentless search for and elimination of all sources of infection. To remove infected teeth and tonsils is often insufficient. In the obscure cases a thorough investigation of the sinuses, prostate, cervix, colon, gall-bladder, and appendix must be made. Suspicion of infection frequently justifies radical treatment. This form of the disease is so insidious and leads to such crippling deformity that temporizing measures are not justifiable.

Only too frequently do we see cases in the clinic of severe disabling infectious arthritis in which buried tonsils, full of pus, have been dallied with for years because of the smallness of their size. The appearance of a tonsil, especially on a casual examination, is extremely deceptive. If any doubt exists about a tonsillar infection, one should err on the side of radical treatment rather than on the side of caution. Our most dramatic results have followed tonsillectomies in young subjects. As for the removal of intra-abdominal foci, one must proceed more conservatively. Gall-bladders and appendices should not be removed unless definite evidence is present of pathology in these organs. In our series of 200 cases the gall-bladder was considered a focus of infection in 6 cases; the appendix in only 1 case. This shows the rarity of appendicular infection in arthritis. The gall-bladder is not infrequently a focus of infection in middle-aged women who are suffering from arthritis. In those cases in which the clinical evidence of cholecystitis is substantiated by a positive Graham test, surgical intervention is indicated without delay.

Beside the removal of foci of infection, which should be done as soon as practicable after the onset of the disease, physiotherapy is of great value in hastening recovery and securing the return of function in partially ankylosed joints. The usual procedure has been radiant heat for from fifteen to twenty minutes, diathermy for twenty minutes, massage and passive movements when indicated. In an earlier communication Cecil and Hansson[15] have described in detail our experience with physiotherapy.

A word as to vaccine therapy. The only vaccines we have thus far found to be of any value are: (1) The autogenous vaccines prepared from the deep crypts of the tonsils directly after tonsillectomy and administered subcutaneously for several weeks thereafter, and (2) the stock gonococcus vaccines in gonococcus arthritis. As for the former, while it is difficult to evaluate the rôle of the autogenous vaccine apart from the result of a tonsillectomy, it seems to be of definite value. As for the gonococcus vaccines they are of distinct value and should always be

employed in this type of case; if practicable they may be used intravenously. Stock vaccines of Streptococcus hæmolyticus and viridans are of very little benefit to the patient. "Immunogen," the new Parke Davis vaccine for arthritis, is of no value. Burbank's[16] method of vaccine therapy, which depends on his complement-fixation test for streptococcus antibodies in the blood, is a form of non-specific treatment not superior to any other form of foreign protein therapy. It is of questionable value in the infectious forms of arthritis and certainly of no value in the non-infectious cases.

In the non-infectious type the removal of foci of infection is not a specific treatment. While one cannot deny that the removal of definite foci of infection in any chronic disease is justifiable, as far as its effect upon the prognosis of the non-infectious type of arthritis is concerned, little is to be expected. The day that witnessed the indiscriminate removal of teeth in middle-aged and elderly people with degenerative arthritis has already passed. Both physicians and dentists, warned by bitter experience, are wary of this procedure, and now remove only abscessed teeth as indicated by the *x*-ray.

The problem of therapy in menopause arthritis is intimately concerned with perverted metabolism and endocrine dysfunction. In this connection it must be pointed out that thus far there is no direct laboratory proof of a hypothyroidism in this condition. In spite of the belief of the English investigators that we are dealing with a condition of hypothyroidism, many of these patients show an increased metabolic rate. It is true that in a good many cases a low reading is obtained and that these patients are benefited by the use of thyroid extract. It is equally true that the fairly constant beneficial results which follow the use of the syrup of hydriodic acid probably depend on the stimulation of the thyroid gland. However, there is no convincing evidence at hand that degenerative arthritis is due to a hypothyroidism.

We have also used the extracts and the desiccated products of the thymus, pituitary, and ovarian glands. Negative results have followed their exhibition. Considering our admitted lack

of knowledge with reference to these latter preparations, and, for that matter, the unsatisfactory status of endocrinology in general, we cannot draw any definite conclusions as yet with reference to the possibilities of specific endocrine therapy in this disease.

Dietetic treatment is of great importance in the management of the arthritis of the menopause. This is one form of the disease in which a low-carbohydrate diet with consequent reduction in weight is of distinct value. We have been accustomed to use a 1250-calorie diet consisting of carbohydrates 40, proteins 80, fats 85. In extreme cases of obesity we have used a 750-calorie diet of carbohydrates 20, proteins 65, fats 45. In the patients who have coöperated, marked reduction in weight has followed, except in a few cases which probably correspond to the "constitutional type" of obesity described by Strouse.[17] We have been fortunate in these cases in securing the coöperation of our obesity clinic in which an intensive effort is made to have these ambulatory patients adhere to their diet.

In addition to the dietetic and drug treatment of this condition, we have always instituted a regular course of physiotherapy. While it is quite true that physiotherapeutic measures *per se* have no specific action on the diseased joints, they are extremely valuable. Their modus operandi is twofold. They act as analgesic agents and probably improve the circulation in the articular arteries by producing a local hyperemia. If we agree with the concept of Hoffa and Wollenberg[18] that in degenerative arthritis there is present an endarteritis obliterans of the articular arteries, then the improvement so often observed clinically, following physiotherapy, rests on a definite basis.

The problem of treatment in the menopause type of arthritis centers about the speeding up of the metabolic activities. A régime consisting of a low-carbohydrate diet, iodids, and, where indicated, thyroid extract, aided by the judicious and skilful use of physiotherapy, will prove of much more benefit to the patient than the removal of foci of infection. The results of treatment in these cases vary directly with the faithfulness of the patient and the persistence of the physician.

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CLINIC OF DR. GAYLORD W. GRAVES

FROM THE DEPARTMENT OF DISEASES OF CHILDREN, COLUMBIA UNIVERSITY, COLLEGE OF PHYSICIANS AND SURGEONS

SHOE-DYE POISONING

Case Report.—E. P., a five-year-old Jewish girl, with negative family history and a previous history without bearing on the present illness, was brought to Bellevue Hospital at about 4 P. M. February 2, 1927, in a condition of partial collapse. Until 2 P. M. on the same day she had appeared well. Shortly after that hour she developed a headache while riding on the subway with her mother and at about 3.30, as she was leaving a restaurant where she had just partaken of an ordinary dinner, she remarked as she glanced at herself in a mirror that the light was peculiar and at the same time appeared to her mother to have lost her normal color. A few minutes later at the entrance to a department store across the street, the little girl collapsed and became momentarily unconscious. Thereupon the ambulance was summoned.

Examination upon her admission to the hospital showed that the patient who was unusually well-nourished and presented no abnormal signs except those referable to her acute condition, was still in a condition of semistupor and circulatory weakness. The temperature was 98° F.; the pulse-rate, 104; and the respiration rate, 20. The quality of the pulse was not good and the heart action was a bit irregular. A soft systolic murmur was reported by one observer to be audible at the cardiac apex and along the left sternal border; but a few hours later the presence of this murmur could not be confirmed. The breathing was unobstructed and the lungs were clear. The predominant symptom was a general cyanosis of an extreme degree most apparent in the lips, tongue, and finger-tips. A complete blood-count was not at first obtained, but a leukocytosis of 20,000 and a hemoglobin content of 82 per cent. were recorded. The urine showed a trace of albumin but nothing else of pathologic significance.

At 8 P. M. the drowsiness or semistupor which had persisted from the time of admission was still very marked and the cyanosis had not perceptibly abated. The heart rate remained at about 100, but weakness and irregularity still characterized the pulsations. Digifolin (½ c.c.) had been given hypodermically at 6 P. M. and at about 8 P. M. 2 grains of caffein sodiobenzoate and 1/100 grain of atropin sulphate were administered in the same way. Shortly

after receiving the latter medication, while in a mustard bath, the child sat up and responded in monosyllables to questions, but her cyanosis persisted with little if any diminution. At this juncture it seemed probable that her condition might be due to some extrinsic toxic agent and renewed efforts were made to obtain from the mother details which would explain the case.

In actually arriving at a diagnosis consideration was given particularly to the following:

1. A negative cardiac history vouched for by a physician who had previously been acquainted with the patient.
2. The extreme suddenness of onset of the illness.
3. The lack of any interruption in the cyanotic state.
4. The writer's personal recollection of two painters at one time admitted to Presbyterian Hospital, New York City, in a similar condition due to their inhalation of the fumes of a benzol-containing paint-remover which they had used on the floor of a closed room.
5. A recent editorial in the Journal of the American Medical Association, which will presently be cited.

After answering negatively all questions relating to gas, headache powders, paint, radiator enamel, and foods, the mother finally recollected that just before leaving home at 2 P. M., the little girl had donned a pair of freshly dyed *suede* shoes, which might have had their black bath at the shoemaker's only shortly before being worn, and which, until they were actually put on, reposed in a closed paper bag.

A sample of 120 c.c. of the patient's blood removed by venipuncture, about 9 P. M., was noted by Dr. Lyttle, the attending pathologist, to be of a hue almost like that of mahogany. This was reported to contain methemoglobin and to give a negative test for carbon monoxid. Other findings were: Serum protein, 7.6; plasma protein, 7.9; cell volume, 33.3; chlorids, 608; uric acid, 3.2; phosphates, 4.3; acetone, 0; Van den Bergh test, direct method, 0; indirect method, +.

At 11 P. M. 250 c.c. of blood was transfused from the patient's grandfather. Thereupon her appearance underwent an almost immediate transformation, the pink color rapidly returning to her cheeks and mucous membranes. Next day her leukocyte count had fallen from 20,000 to 14,600, with 60 per cent. of polynuclears, and the urine was negative except for a trace of acetone. On the second day after admission she was able to go home.

A qualitative analysis of the shoe-dye revealed the presence of anilin, alcohol, and benzene.

Comments.—Reports of poisoning from dye containing anilin or nitrobenzene have been most frequent in the United States since the World War, at which time the dye industry first assumed importance in this country. Sixteen cases of shoe-dye poisoning among soldiers at Camp Johnston, who had had their shoes and puttees dyed with a nitrobenzene preparation, were reported in 1919 by Stifel,[1] who subsequently added to his

series another case referred by Herrick[2] from Camp Jackson. In 1925 Muehlberger[3] reported 9 cases of shoe-dye poisoning due to anilin instead of nitrobenzene and in connection with this report cited the records of 47 other cases of shoe-dye poisoning (published during the previous twenty years from both Europe and the United States), appending references to the literature recounting the ill-effects of hair-dye, paints, and even laundry inks. Hamilton[4] has made a detailed study of such cases.

Muehlberger notes that shoe-dye poisoning is induced by the solvent of the pigment and that this is absorbable through intact skin sufficiently to cause cyanosis, even without discoloration of the skin. It would seem that the perspiring condition common to the feet would favor such absorption. Both Rosenau[5] and Hamilton[6] emphasize the greater importance of skin absorption of anilin and nitrobenzene notwithstanding the fact that poisoning from the fumes may occur. Both anilin and nitrobenzene ultimately produce effects which are almost identical.

The whole subject is rendered particularly difficult for the clinician at the present time because of the apparent conflict in scientific reports relating to the action of these compounds. Most writers, including Rosenau,[5] affirm the existence of methemoglobinemia, with resulting cyanosis in poisoning from anilin and nitrobenzene. Young, Muehlberger, and Meek,[7] however, contend that methemoglobin is not, as a rule, found in such cases, and that actual death from anilin poisoning is cardiac in character. This they believe to be demonstrable by electrocardiographic studies showing an effect of anilin on the conducting tissues of the heart in the occurrence of arrhythmias and heart-block. If this view be correct, transfusion, obviously, would not be indicated.

Chandler[8] records chromatolytic degeneration in the Purkinje cells of the cerebellum as the result of nitrobenzene poisoning induced experimentally and emphasizes the occurrence of a free interval observable between the absorption of the nitrobenzene and the onset of the symptoms. Curschmann[9] states

that methemoglobinemia may be demonstrable spectroscopically only early in a case, before the occurrence of cyanosis.

The methemoglobinemia problem is made still more complex by the occasional occurrence of sulphemoglobinemia of enterogenous origin induced by reducing substances, as nitrites; such an effect, for example, being induced by the coincident administration of phenacetin and sulphur, or nitrobenzene and sulphur.

With the clinical evidence at hand a physician confronted by a case of cyanosis, induced by a benzol derivative, would be justified in considering as highly probable the existence of anoxemia due to blood changes, in conjunction with the toxic effect of the chemical on the heart-muscle, to which latter action Muehlberger and his associates have assigned first importance. Considered on this basis, the procedure followed in the case here reported would seem to be rational whenever the symptoms induced appear equally serious. Certainly the uninterrupted cyanosis noted clinically in such cases over a period of many hours seems more typical of blood changes resulting in oxygen deprivation of the tissues than of circulatory failure. With more laboratory observations on human cases the question of the advisability of transfusion will eventually not be difficult to answer more conclusively.

The Chicago Health Department, whose rules regulating the use of shoe-dyes have been cited in the Journal of the American Medical Association, July 3, 1926, has decreed that all recently dyed shoes should stand in the open for seventy-two hours before being worn and that canvas and satin shoes under no conditions should be dyed. Such a ruling in some form should be universal. It might well be supplemented by a provision for better warning labels on all preparations containing "oil of mirbane" or anilin, whether these be shoe-dyes, paint-removers, solvents and cleaning agents, perfumes, or so-called disinfectants. Finally, it should not be forgotten that among ignorant retailers there is always the danger of substitution and "bootlegging" practices, rendering it not strange for a container of a supposedly non-toxic dye or solvent to hold a benzol derivative deserving of caution.

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CLINIC OF DR. HORACE S. BALDWIN

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THE CLINICAL COURSE AND TREATMENT OF PNEUMONIA AS RELATED TO THE PNEUMOCOCCUS TYPE

THE biologic classification of pneumococci into types based on their ability to produce specific agglutinins, precipitins, and protective bodies, by Neufeld and Lister abroad and by Dochez and Gillespie in this country, has been a great stimulus to the study of pneumonia and the perfection of an efficient serum treatment for the disease. As a result of the work of these investigators, three dominant biologic types of pneumococcus have been found, each possessing specific and characteristic immune reactions. These three types have been referred to as Types I, II, and III. The other group has been referred to collectively as pneumococci Type IV. This group is really an assembly of all other types of pneumococci, many of them just as distinct as Types I, II, and III.

Little effort had been made to correlate the type of pneumococcus with clinical manifestations, complications, and other features of the disease, until a series of 2000 patients with lobar pneumonia was studied in the wards at Bellevue Hospital from this standpoint by Cecil, Larsen, and myself. What I shall say concerning the clinical peculiarities of the various types of pneumococci is derived largely from that investigation.

Let us first consider the clinical characteristics of pneumococcus Type I pneumonia. This type in our series occurred in 33.6 per cent. of our pneumococcus pneumonias. It is most apt to occur in young people. In patients under thirty years of age, 42 per cent. had pneumonia due to pneumococcus Type I, while in those over sixty years of age only 20 per cent. were due

to pneumococcus Type I. In considering the history of the patient preceding the onset of the pneumonia, it is less common to find a history of preceding infection of the respiratory tract in pneumococcus Type I pneumonia. Thus in our series, whereas the histories gave definite evidence of preceding respiratory infection in at least 46.7 per cent. of all our pneumonias, in the Type I group the incidence of preceding infection was only 36 per cent. Onset with chill and pain in the chest is much more common in Type I pneumonia, being 70 to 80 per cent. in our series, and it is very rare in pneumococcus Type I pneumonia not to have clear-cut physical signs of lobar consolidation and rusty sputum. Also, the phenomenon of crisis is more common in pneumococcus Type I pneumonia than in other types, 56.6 per cent. of our Type I pneumonias resolving by crisis. Concerning the complications, it was found that in the pneumococcus Type I cases the percentage of incidence of empyema, pericarditis, endocarditis, meningitis, arthritis, phlebitis, and peritonitis was nearly double (12 per cent.) compared to other types. The mortality in our cases was 20.7 per cent. So, concerning Type I pneumonia it is more apt to be typical—onset abrupt, with chill, pain in the chest, rusty sputum, tending to resolve by crisis, characterized by the typical pneumococcus complications and accompanied, when untreated with a specific agent, by a mortality of 20 per cent.

The pneumococcus Type II occurred in 19.1 per cent. of our cases of pneumonia. It is the most virulent of all pneumococci. Like the Type I pneumonia, it is apt to have a sudden onset with chill and pain in the side, and to terminate by crisis. Rusty, bloody sputum is very common. Concerning age-incidence, the predisposition for attacking the young is not so marked as in Type I. In our series of cases, 20 per cent. of the pneumonias under forty years were due to pneumococcus Type II, while of those over fifty years of age 23 per cent. were due to pneumococcus Type II. The clinical course is practically always severe—although there are exceptions. The mortality in our series was 42 per cent. In other words, out of 221 patients with pneumococcus Type II pneumonia, 93 died.

So, in general, it may be said that the typical classical cases of pneumococcus pneumonia are represented best by the pneumococcus Types I and II group. These comprised 42.7 per cent. in our series, with an average mortality, combined, of 24 per cent.

The pneumococcus Type III comprised 13.3 per cent. of all our pneumococcus pneumonias. It has some very interesting clinical peculiarities. First, it is very common to find a history of preceding respiratory infection, 60 per cent. of our Type III cases showing this. Also, the onset is usually gradual without an abrupt chill, pain in the chest, and sudden prostration. Rusty typical pneumonic sputum is usually absent—usually the sputum is thick, greenish purulent material of considerable tenacity. Pneumococcus Type III tends definitely to attack people in the second half of life, and particularly those broken down by chronic constitutional disease. In our series, under fifty years of age, pneumococcus Type III occurred in only 4.3 per cent., compared to 24.1 per cent. over fifty, and 33.7 per cent. over sixty years of age. And, whereas in all our cases of pneumonia systemic disease occurred in 32.6 per cent., in the Type III group 63.3 per cent. were subjects of chronic systemic disease. The pneumococcus Type III apparently has a predisposition for the female—especially over fifty years of age. In men over fifty years of age the incidence was 17.1 per cent. In women over fifty years of age the incidence was 36.1 per cent. The general mortality for pneumococcus Type III pneumonia was 41 per cent. In cases uncomplicated by systemic disease it was 8 per cent., with systemic disease, 64 per cent. So, one may say that in previously healthy adults pneumococcus Type III is not necessarily a severe pneumonia.

It is hard to generalize concerning pneumococcus Type IV pneumonia. In a large series it will average 33.1 per cent. It plays little favorite with age. It is the pneumonia secondary to preceding respiratory infection. In general, its onset is like that of pneumococcus Type III, and cessation by lysis is the rule. Typical signs and rusty sputum are less apt to occur. The average mortality is not so light as is generally supposed, being 29.2 per cent. in our series.

Concerning the factors most important in determining the prognosis in pneumonia, I should list the following: Age, alcoholism, pre-existing systemic disease, the type of pneumococcus present, and the presence or absence of bacteremia.

Before considering the present status of specific therapy, just a few words about bacteremia. In a series of 107 patients in whom blood-cultures were taken at frequent intervals during the course of the disease, in some instances every day, the cases showing positive blood-cultures had a mortality of 83.1 per cent. as opposed to 18.7 per cent. in the cases showing sterile blood-cultures. Figure 119 shows in detail the mortality associated with bacteremia in the various types of pneumococci. We may say, therefore, that bacteremia in pneumonia is associated with a bad prognosis.

DEATH-RATE IN CASES WITH STERILE BLOOD-CULTURE

Type.	Cases.	Fatal.	Per cent.
Pneumococcus I	92	14	15.2
Pneumococcus II	47	8	16.2
Pneumococcus III	26	11	41.5
Pneumococcus IV	75	12	16.0
	240	45	18.7

DEATH-RATE IN CASES WITH POSITIVE BLOOD-CULTURE

Type.	Cases.	Fatal.	Per cent.
Pneumococcus I	33	24	72.7
Pneumococcus II	31	28	90.3
Pneumococcus III	10	8	80.0
Pneumococcus IV	15	14	93.3
	89	74	83.1

Fig. 119.

Now, consider the other side of the picture. Figure 120 shows the relationship between the development of protective bodies in the blood-serum of the untreated patient and prognosis. It will be observed that protective substance is associated with recovery, its absence with death. Also, and very important, one hardly ever finds the protective substance in the blood-stream at the same time the blood contains pneumococci. These two phenomena are antagonistic.

PROTECTIVE BODIES AND PROGNOSIS

	Cases.	Died.
Showing protective bodies during course	20	3
Showing no protective bodies during course	5	5
Showing definite protective bodies day of death	2	
Protective bodies present with empyema	3	

Fig. 120.—Relationship between the development of protective bodies in the blood-serum of the untreated patient and prognosis.

Specific therapy in pneumococcus pneumonia attempts, by artificial means, to establish and maintain a balance of protective substance in the blood-stream of the same type as that of the organism causing the disease.

At present, we have an extract of protective substance against pneumococcus Type I and pneumococcus Type II, developed by Felton of Harvard, which conforms to the necessary requisites. Using this extract in amounts of 5 to 20 c.c. it is possible to confer a protective balance in the blood-stream and clear up the bacteremia.

This extract is made by concentrating the protective substance present in immune horse-serum. It is a thin, opalescent solution which contains enough horse-serum to sensitize and occasionally cause mild serum sickness.

Since 1925, this concentrated extract has received considerable clinical trial at Bellevue, Boston City, Harlem, and the New York Hospitals. The frequency of chill reactions associated with its use has been markedly reduced until, today, the great majority of the lots produced by Felton are free from any severe deleterious chill substance. Also, and of great importance, the concentration of the antibodies has been greatly increased. Felton now expresses the concentration of his product in terms of units. A unit of antibody is ten times the smallest amount of antibody that will protect a mouse against 100,000 fatal doses of a highly virulent culture. A fair idea of the progress he has made in concentration may be gained if one realizes that whereas an immune Type I or Type II whole-serum to pass the Federal regulations must contain 50 units per c.c., Felton has been able to make a Type I concentrate that contains

4000 units per c.c., and a Type II concentrate that contains 1200 units per c.c.

In addition to increasing the concentration and minimizing the frequency and the severity of the chill reaction, a polyvalent Type I and Type II concentrate is now being used, thus lessening the delay in giving antibodies to a probable Type I or Type II pneumonia. Thus far, little progress in the production of a Type III concentrate has been made, and no clinical trial has been carried out. As for the heterogeneous Type IV group, we

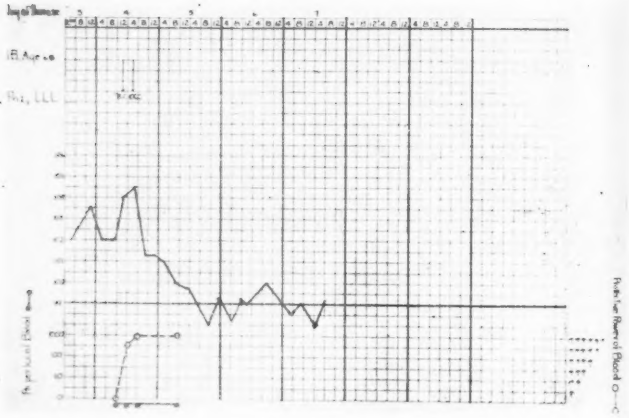

Fig. 121.—Type I pneumonia. Patient entered hospital on third day of disease and was treated with Type I concentrate. The temperature curve is represented by the unbroken top line. Below the temperature curve, the broken line represents the amount of protective substance present, the unbroken line the presence or absence of bacteremia.

are still far from any specific form of therapy, although investigations into the possibility of subdividing this group are in progress and seem promising.

Figure 121 shows a Type I pneumonia who entered the hospital on the third day of the disease. On the morning of the fourth day he was given 7 c.c. of Type I concentrate. No protective substance was present at the time the concentrate was given. The blood-culture was sterile throughout. Immediately following the administration of the antibody solution, a protec-

tive test of the patient's blood showed a large amount of protective substance present. This was maintained. Shortly following a further dose of 10 c.c. the patient's temperature dropped by crisis. The temperature curve is represented by the unbroken top line. Below the temperature curve, the broken line represents the amount of protective substance present, the unbroken line the presence or absence of bacteremia.

Figure 122 is that of a Type I pneumonia, entering the hospital on the first day of illness. Blood taken for culture and

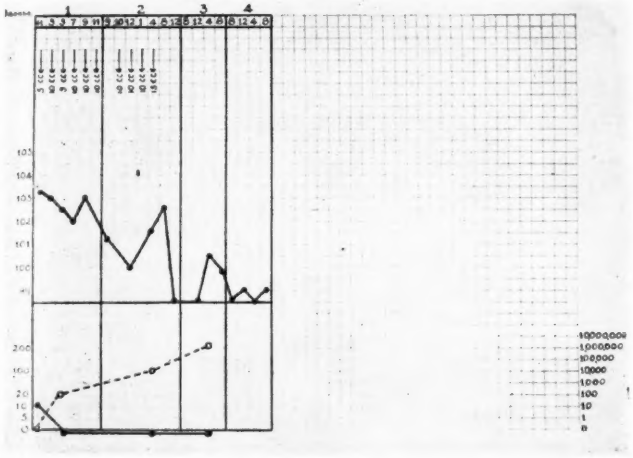

Fig. 122.—Type I pneumonia. Patient entered hospital on first day of illness, treated with Type I concentrate.

protective substance previous to the administration of concentrated Type I antibody showed ten colonies of pneumococci Type I per c.c., and no protective substance present. Six hours later, following the administration of 15 c.c. of Type I concentrate, the blood-culture was sterile and a protective balance had been established. A marked drop in temperature occurred on the second day. The blood-culture remained sterile; the protective substance increased in concentration, and the patient made an uneventful convalescence.

The preceding case reports show how it is possible, by giving comparatively small amounts of Felton's Type I concentrate, to produce a protective balance in the blood of a patient with Type I pneumonia and sterilize the blood in the presence of a bacteremia of a moderate degree.

The great propensity of pneumococcus Type II to invade the blood-stream made it practically impossible, previous to the development of Felton's concentrate, to treat this severe type of pneumonia adequately. The mortality associated with bac-

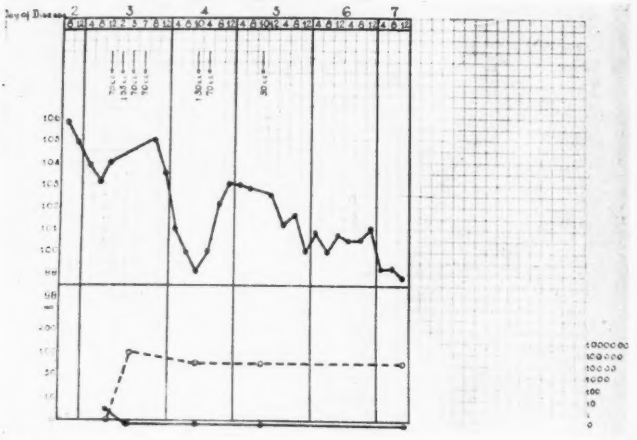

Fig. 123.—Patient with Type II pneumonia treated with Type II immune serum.

teremia in Type II pneumonia varies in untreated series from 70 to over 90 per cent. During the winter of 1926 at Bellevue Hospital we were able to show that by using a very potent Type II immune serum prepared by Dr. Park of the New York City Board of Health, bacteremia could be cleared, a protective balance established, and recovery occur.

Figure 123 furnishes an example of this. It will be seen that the patient on the third day of his illness had five colonies of pneumococci Type II per c.c. No protective substance was present. He was given several doses of Type II immune serum.

Shortly afterward, a blood protective balance to a considerable extent was demonstrated. The blood-culture was sterile, and a marked drop in temperature and an improvement in the patient's general condition occurred.

The next patient (Fig. 124) with pneumococcus Type II pneumonia in whom treatment was begun on the fourth day of his illness with a polyvalent Type I and Type II Felton's concentrate. Just prior to the administration of the concentrate, the blood-culture showed several colonies of pneumococci

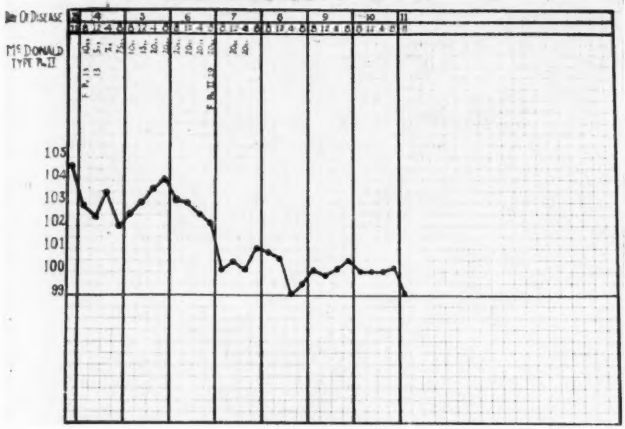

Fig. 124.—Patient with Type II pneumonia in whom treatment was begun on fourth day of illness with a polyvalent Type I and Type II Felton's concentrate.

Type II per c.c. On the morning of the fifth day, after several doses of concentrate, the patient's general condition was much improved, and the blood-culture was sterile. Treatment with large amounts of the concentrate was continued. The patient made an uneventful recovery.

It is important to remember, with regard to the specific treatment of pneumonia, that the pneumococcus elaborates a specific soluble substance which has the property of neutralizing the protective substance to a considerable degree. Naturally,

in cases of bacteremia, the soluble substance is at its highest concentration and patients with a bacteremia require considerably more antibody than those whose blood-culture is sterile. The accompanying chart (Fig. 125) is that of a pneumococcus Type II pneumonia whose treatment with a very strong immune serum was begun on the fifth day in the presence of a bacteremia consisting of 1000 colonies per c.c. It will be observed that, in spite of a considerable amount of serum, the number of pneumo-

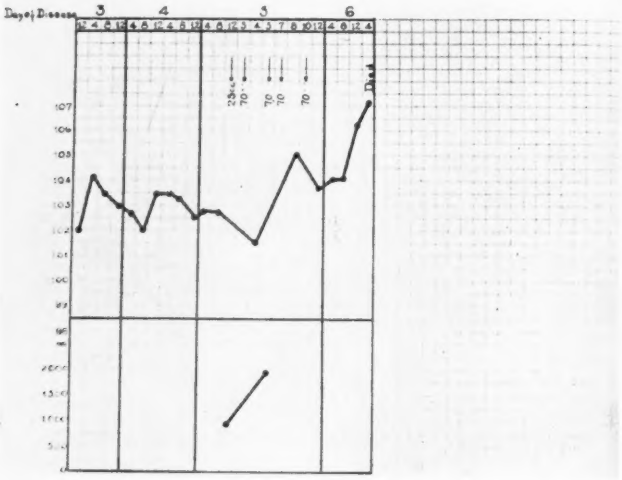

Fig. 125.—Patient with Type II pneumonia in whom treatment with very strong immune serum was begun on fifth day of his illness in the presence of bacteremia consisting of 1000 colonies per c.c.

cocci in the blood-stream increased. No protective balance was established and the patient died on the following day.

With the improved Felton concentrate, we are now observing—especially in Type I cases—a marked clinical improvement. Following the administration of the concentrate the temperature usually falls and, most important, there is an improvement in the patient's general condition. At the New York Hospital its use during the past two years in a carefully controlled series,

THE NEW YORK HOSPITAL

1926–28

Type.	Control series. Cases.	Died.		Treated series. Cases.	Died.	
I	11	2		10	1	
II	13	6		17	2	
III	4	3		5	2	
IV	20	6		22	4	
Total	48	17	35.4%	54	9	16.6%

Fig. 126.—Mortality associated with bacteremia in the various types of pneumococci in detail.

has shown considerable decrease in the mortality. While the statistics at the New York Hospital present a relatively small series, yet they have been consistently good for two years and probably present a fairly reliable picture of the benefit of Felton's concentrate in the treatment of pneumococcus Type I and Type II pneumonia.

CLINIC OF DR. JESSE G. M. BULLOWA*

HARLEM HOSPITAL

BACILLUS SUIPESTIFER (HOG CHOLERA) INFECTION OF THE LUNG

THIS patient came into Harlem Hospital on the Pneumonia Service on July 11, 1927, with the story that he had been ill since the 7th. He complained of general weakness, pain in the right side, and a slight cough with mucopurulent sputum. The sputum had an offensive odor.

The physical signs were those of a consolidation of the right middle lobe. Anteriorly, there were tubular breathing, dulness, increased voice, and breath-sounds, and increased vocal fremitus. There was a friction rub, as well as a few moist râles at the right base, and bronchovesicular breathing.

On admission the temperature was 104.5° F., pulse 100. The temperature fell the next day to 102° F., pulse to 80. On July 12th there were showers of râles at the right base and the patient became actively delirious as the temperature rose to 104.5° F., and the next day went to 105.2° F. The pulse, which had risen to 120, dropped to 110, and the patient suddenly succumbed.

Fluoroscopically, on the day of admission, there was involvement of the right middle lobe. The following day a film showed an area of consolidation at the base of the right pulmonary field and the heart was enlarged to the left. The blood-count was 12,100 white blood-cells, polymorphonuclears 9864, transitionals 363, lymphocytes 1453, and eosinophils 121. On the 13th, the blood-count was 14,750, polymorphonuclears 12,771, transitionals 497, and lymphocytes 1782.

On admission the sputum smear showed a few Gram-positive diplococci, and many motile Gram-negative bacilli. The mouse which was inoculated died with distention of the abdomen which was due to gas-forming organisms. There was an offensive peritoneal exudate and a subcutaneous emphysema. Dr. Julius Kavee recognized the unusual character of the mouse' behavior and saved the organisms recovered. These were finally identified by Carolyn Rosenstein, working with Dr. Krumwiede, as a paratyphoid type belonging to the Bacillus suipestifer (B. choleræ suis) group.

At first it was thought that the gangrenous, gas-forming exudate in the mouse' peritoneum was due to a Welch bacillus which might have escaped from its intestine during the puncture. The recovery of the organism from the

* From the Medical Service, Harlem Hospital, Lewis K. Neff, director the Littauer Pneumonia Fund of New York University, and the Research Laboratory, Department of Health, New York City.

peritoneum of the mouse in the blood-culture of the patient taken during life, and from the lung of the patient by transpleural tapping postmortem, demonstrated the origin of the organism to be from the patient's sputum.

There was no agglutination of the organisms in the peritoneal exudate with pneumococcus sera of Type I, II, or III. The blood-culture taken on admission showed many Gram-negative bacilli in both broth and agar.

The urine on admission showed a slight trace of albumin, and numerous granular casts. There were neither red blood-cells nor leukocytes in it.

This patient was a serum case. At Harlem Hospital, each alternate case receives serum, in order to test the efficacy of refined serum in the treatment

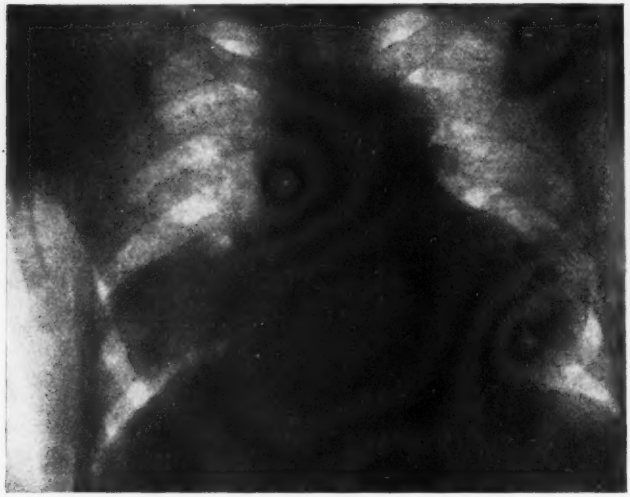

Fig. 127.—Note the very thin shadow in the anterior posterior film. Consolidation of the middle lobe produced by Bacillus choleræ suis. Note also widening of the aortic arch.

of pneumonia. He therefore received 5 doses of Felton's polyvalent antibody solution, preparation 911, intravenously. There was not the slightest chill reaction after any dose.

Following the first dose, the temperature fell, but other doses had no effect upon it.

Without the careful bacteriologic study of patients suffering from the clinical signs of lobar pneumonia, this patient would have been regarded as a failure with serum. The serum could do neither harm nor good, however, in this condition. It was

given before the typing, on the basis of the positive clinical findings. There was unquestionably a consolidation which was confirmed by fluoroscopy and radiograph. The patient received whisky, atropin, and pituitrin. The abdominal distention became a most distressing clinical feature.

The number of cases of pneumonia due to members of the paratyphoid group reported in the literature is not great, and this is the only case of its kind we have observed in over 800

Fig. 128.—For descriptive legend see Fig. 127.

admissions for lobar pneumonia at Harlem Hospital which have been carefully studied bacteriologically.

On admission the patient was unable to give a coherent account of the origin of his illness, and before the bacteria responsible for it were identified, he had lapsed into delirium; his friends were unable to assist us.

The Bacillus choleræ suis is a secondary invader in hog cholera and causes a severe gastro-enteritis, or an enteric fever complex. We are familiar with no case in the literature in which this organism has been identified in the blood-stream and in the

lung. It is possible that the affection may have been due to the infection of food by some infected, uncooked pork. Krumwiede reported a family in which a package of tapioca was infected by pork chops brought from the butcher shop in the same bag with the package of tapioca. Those who partook of the chops, after they were cooked, escaped illness, but those who ate the tapioca that had had contact with the uncooked chops became ill.

No agglutination test was performed on this patient because the diagnosis was not established while blood was still available.

The definite physical findings, confirmed by *x*-ray, at first suggested the diagnosis of pneumonia with attendant acute pulmonary gangrene. It is possible that some of the cases called pulmonary gangrene which, on account of their usual rapid course, are unsatisfactorily studied, may prove in the future, on careful study, to be an infection of the lung caused by a member of the paratyphoid group.

TYPE I PNEUMONIA FOLLOWING SUBMERSION AND WITH EMPYEMA

THE patient, J. M., a pile driver, thirty-three years of age, was admitted to Harlem Hospital on May 25, 1928, complaining of pain in his right chest, dyspnea and a productive cough, since May 22, 1928. On May 14th, he fell overboard. Following this, he had a slight cold, but no other trouble until May 22d. On this day he had a chill lasting twenty minutes and severe pain in his right chest with blood-tinged expectoration. There was pain on breathing.

On admission, he complained principally of pain in his right chest. His temperature was 104° F., his pulse 112, respirations 40. There was increased dulness, and bronchial breathing and bronchophony over the right lower lobe. There were no râles. There was slight epigastric tenderness and distention.

The next morning, there were crepitant râles over this area. The right chest was strapped with elastikon and this gave some relief. On his morning rounds, the house physician noted very marked distress and a complaint of pain which the patient referred especially to the right lower quadrant. There was marked rigidity of both recti and the rebound tenderness was obscured by the rigidity. There was high rectal tenderness on the right side. Because of these symptoms, the tentative diagnosis of appendicitis was suggested.

Blood-culture revealed 6 and 40 colonies on the plates. The patient received a polyvalent Banzhaf serum No. 7 and Sobotka H852 containing 30,000 units of Type I and 8000 units of Type II. An hour after this injection, he had a chill. This serum was being tested for chills. Smaller doses in this and other patients had given none. This patient later received another dose of 10 c.c. or 30,000 units, Type II, without any reaction.

On my rounds, I found the patient lying in bed in the dorsal position with his legs extended. The physical signs were those of a right lower lobe pneumonia with intense consolidation. There were crepitant râles and a pleural friction rub. The abdomen was rounded, the most marked rigidity being in the right upper quadrant. There was no rebound tenderness. There was no Meltzer sign, *i. e.*, no aggravation of the pain on contraction of the psoas muscle (when the thigh was raised with the leg extended) against a steadying hand on the abdomen. There was no hyperalgesia of the third cervical, of the anterior thoracic or sacral segments. There was exquisite tenderness of the seventh posterior thoracic maximum, more marked on the right side. The bladder was distended, the rectum was not ballooned. The tenderness previously noted was not verified; there had been no vomiting. I concluded that the patient was suffering from reflex spasm of the abdominal muscles in association with his pneumonia. Irritation of dermatome was revealed by testing for hyperalgesia—the corresponding myotome response is increased muscle tonus.

In almost every hospital, patients suffering from pneumonia are at times admitted for abdominal intervention by the surgeon. We have had the experience in our own service of having patients admitted for pneumonia who actually had acute abdominal conditions. Once it was gastric ulcer, again a gangrenous appendicitis. The association of muscle spasm with thoracic hyperalgesia involving the seventh posterior thoracic maximum is an important differential point. In appendicitis the hyperalgesia usually involves the eleventh anterior thoracic maximum. This is in the right lower abdominal quadrant. Increased tonus of the muscles as a response to visceral disease is an important guide. In fact, this segmental increased tone is the basis of many of our diagnoses.

After the first dose of serum, the patient's temperature fell to 100° F., the pulse to 104, and the respirations to 24. When the result of the blood-culture was known, additional doses of serum were given, in all some 85,000 units of Type I. The patient was rated at 40: there was subtracted from 100, 5 for involvement, 5 for rate, 5 for pleurisy, 5 for sleeplessness, 5 for circulatory efficiency and cyanosis, 10 for distention, and 5 for vomiting.

The following morning, although the temperature was normal, the patient was delirious and continued so for several days. He improved, and the temperature continued relatively low, reaching 100° F. on the eighth day after admission. Then the temperature commenced to rise, and he complained of pain in the arms and legs. At this time, it was thought that the temperature rise was due to serum sickness as it had come on nine days after the first injection. There was dulness over the right side posteriorly to the middle of the scapula, with absence of breathing, and diminished voice. The heart was not displaced. There was a complaint of pain in the arms and legs persisting for four days. The blood-counts were: White blood-cells 16,000 on admission, 20,000, 13,920, and 20,800. As the temperature did not subside, it was concluded there was fluid in the chest. The blood-count had fallen to 9800 on the seventh day and on the tenth was 19,600. On the tenth, 10 c.c. of purulent fluid was withdrawn. Before operation, it was determined that there was an excess of antibody of Type I in the blood-stream by the antibody detection test. This test is performed by rolling the patient's serum with a standard emulsion of bacteria of specific type, and observing their agglutination in the presence of antibody.

An *x*-ray examination June 4th showed a homogenous clouding of the entire right pulmonary field without displacement of the heart.

It has been our experience that the Type I pneumococcus is the organism which most frequently produces a pleural pneumonia, and that those cases in which there has been a violent pleurisy at the onset are most frequently associated with empyema. In spite of the fact that this patient had ample antibody in the blood, he continued to run a temperature up to 103° F. The respiratory and pulse rates were no longer increased. In these cases, the fibrin, which is deposited with the initial invasion, acts

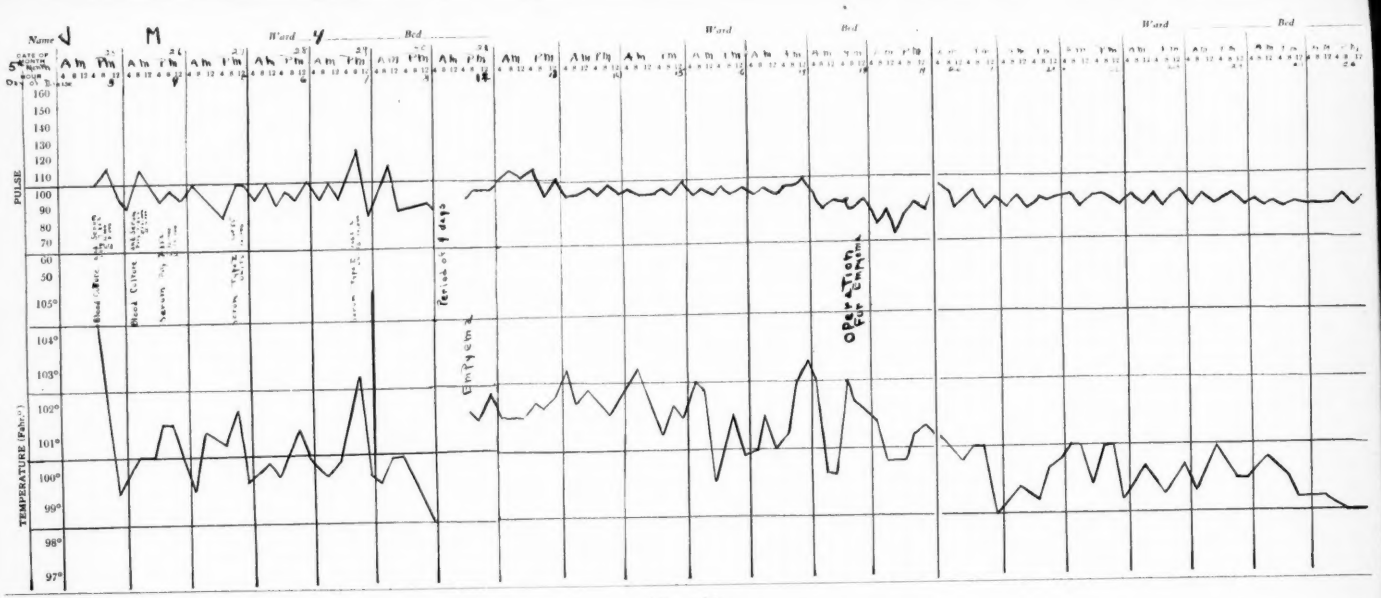
Name
Ward
Bed
PULSE
TEMPERATURE (Fahr.)
Empyema
Operation for Empyema

Fig. 129.

as a foreign body. An exudate of pus is formed in a futile attempt to discharge it. Surgical intervention becomes necessary. It has been thoughtlessly said that the number of empyemata are more numerous in our serum series, and this is probably true, as the patients are more apt to survive for the required intervention.

LOBAR PNEUMONIA TYPE II TREATED WITH FELTON AND BANZHAF AND SOBOTKA'S ANTIBODY SOLUTION

I AM about to narrate the story of a patient who was admitted to the Pneumonia Service of Harlem Hospital on January 30, 1928. His chief complaints were cough, chill, fever, chest pain, and weakness.

The onset was on Monday, January 23d, at 9.30 P. M. One month prior to onset the patient contracted a cold on the chest. He attributes this to the frequent changes in temperature incident to his work as a mixer of dough, carried on within several feet of the bake ovens. During this month he had a slight cough and head cold. On one occasion, about a week before the onset of the present illness, the sputum was blood streaked. There were no night-sweats and no fever during this period. On the night of onset, while he was preparing for bed he began to feel very hot and feverish. As soon as he was in bed, he was seized with a violent chill lasting three minutes, which was repeated in an hour. His cough became severe and more productive, so severe, in fact, that he was kept awake all that night. Soon after his initial chill, he felt a very sharp, severe pain localized on the left side over the precordium. Pain was felt, also, over the lower portion of the right chest. The fever, cough, and pain continued throughout that day. The following morning a physician was called. His diagnosis was bronchitis.

The temperature at this time was 104° F. During the night of the 25th the pain in the right side (up to this time it had not been as bad as on the left) became sharper and more constant, and was now considerably worse than the pain on the left side. During Thursday, the 26th, the sputum contained streaks of blood on several occasions. From that time until his admission, his condition continued unchanged. There were no further chills after Thursday (the fourth day), and the sputum was not blood stained. With the onset, there was a severe frontal headache which disappeared on the following day. The patient said he had become increasingly weak.

He is a Porto Rican. He had malaria in 1924. There is no history of previous pneumonia. Since the onset, patient has had to void once or twice at night. He does not drink or smoke, and has been in New York City only ten months, coming directly from Porto Rico. His parents are living and well.

Physical examination discloses a young, Spanish-speaking Porto Rican who lies quietly in bed, quite pale and very markedly prostrated. The conjunctivæ are pale, the pupils are round, and react to light and accommodation. There are no petechiæ. The lips are very pale. The teeth are in fair condition. The tongue is moderately coated. There is dulness and bronchial breathing with exaggerated voice over the right scapular and infrascapular regions, and high in the right axilla. These findings, together with round, crepitant râles, are also heard over the left lower lobe. In addition, there is a pleural rub over the seventh to the ninth spaces in the anterior portion of

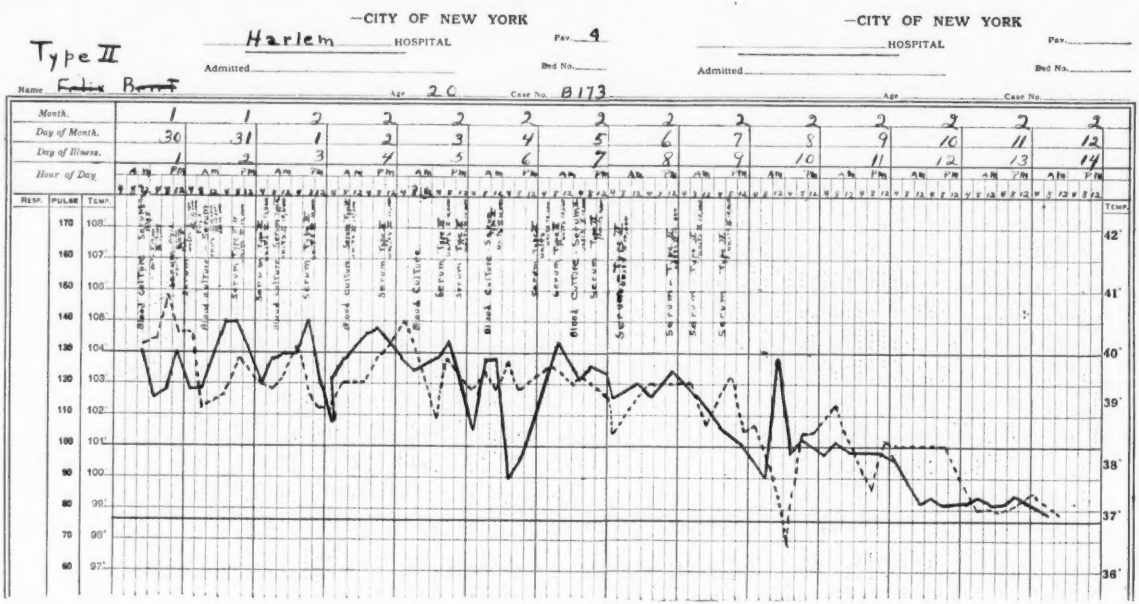
—CITY OF NEW YORK
Type II
Harlem HOSPITAL
Pav. 4
Admitted
Bed No.
Name
Age 20
Case No. B173
—CITY OF NEW YORK
HOSPITAL
Pav.
Admitted
Bed No.
Age
Case No.
Month.
Day of Month.
Day of Illness.
Hour of Day
RESP.
PULSE
TEMP.
Blood Culture
Serum Type II
Serum - Type II
Serum Type II

Fig. 130.

the left axilla. The maximum impulse of the heart is in the left fifth interspace within the left midclavicular line. The sounds are very loud, the rate 130 and regular. There are no murmurs. There is no abdominal distention. The finger-nail beds are white and pallid. Knee-jerks are not elicitable.

Diagnosis.—Lobar pneumonia involving the right upper and the left lower lobe, confirmed by radiography.

On examination, the urine was acid, with albumin present, and there was an occasional epithelial cell. Specific gravity 1.010. The leukocytes were 6400, of which 84 per cent. or 5376 were polymorphonuclears, and 16 per cent., or 1024, lymphocytes. The erythrocytes were 3,370,000, and the hemoglobin 55 per cent. A Kahn test was negative. Blood-pressure 100/38.

On admission, the sputum was white and tenacious, revealing many Gram-positive diplococci which were bile soluble, of Type II, and agglutinated positively in 1:1 and in 1:10 dilutions. They also showed precipitation for Type II. A supravital stain the next day showed 13,600 leukocytes, of which 87.5 per cent. were active, 7.5 per cent. rounded, and 1.5 per cent. non-motile polynuclears. The lymphocytes were 3 per cent., mononuclears 0.5 per cent. On one occasion, the coagulation time was 240 seconds before the serum and 225 seconds afterward. On two other occasions, the coagulation time was 370 and 190 seconds, respectively. A blood-culture made with 3 c.c. of blood diluted 1:10 revealed 24 colonies per cubic centimeter in one plate, and 32 colonies in another.

The patient was rated at 40 in the Harlem Hospital rating plan, which means that there was 40 per cent. of health remaining. There was subtracted from 100, the indicated amounts:

Respiratory: Involvement (10), rate (5), pleurisy (5).

Nervous condition: Headache (0), irritability (0).

Sleeplessness (0), delirium (0), apathy (0), coma (0).

Circulatory efficiency: Rate (10), cyanosis (0).

Gastro-intestinal: Distention (5), vomiting (0).

Complications: Special factors: Anemia (5), bacteremia (20).

On admission, as soon as the blood-culture was taken, this patient was tested for serum sensitiveness by dropping a single drop of normal horse-serum into his eye. There was no reaction in twenty minutes. We test our patients with either normal horse-serum or the serum to be injected to discover their relative insensitivity to horse-serum. The patient then received 10 c.c. intravenously of a polyvalent Felton serum, containing 15,000 units of Type I, 10,000 units of Type II, and 10,000 units of Type III. At 9.30 that night—that is to say, six hours later—he received 14,000 units Type I, 9600 units Type II, and 12,000 units of Type III.

The following morning the result of the typing was known, and after that he received two doses of Type II serum, usually 18 c.c., containing 800 units per cubic centimeter or 14,400 units. He was placed in an oxygen tent, and oxygen at 30 volumes per cent. was administered continuously that day. At eight-hour intervals the next day, he received three doses of Type II serum, 14,400 units, 16,000 units, and 9000 units. There was no reaction, and apparently no marked effect upon the temperature, although his condition improved somewhat. The pleurisy on the right side was quite marked. He

Fig. 130.

was strapped with elastikon. On the next day, because of a temporary shortage in specific Type II serum, he was given the polyvalent serum, and received the following doses:

February 2d,	10.30 A. M.:	Polyvalent No. 13	Felton Serum
		Type I, 16,500 units	
		Type II, 11,000 "	
		Type III, 11,000 "	
	7.00 P. M.:	Polyvalent No. 13	" "
		Type I, 22,500 units	
		Type II, 15,000 "	
		Type III, 15,000 "	
February 3d,	3.00 A. M.:	15 c.c. polyvalent No. 13	" "
		Type I, 22,500 units	
		Type II, 15,000 "	
		Type III, 15,000 "	
	12.15 P. M.:	10 c.c. polyvalent No. 13	" "
		Type I, 15,000 units	
		Type II, 10,000 "	
		Type III, 10,000 "	
	8.15 P. M.:	Type I, 15,000 units	" "
		Type II, 10,000 "	
		Type III, 10,000 "	
February 4th,	1.20 P. M.:	Type I, 15,000 units	" "
		Type II, 10,000 "	
		Type III, 10,000 "	
	5.45 P. M.:	Type II, 18,000 units, 20 c.c.	
		Type III, 4,200 units, 7 c.c.	
February 5th,	2.00 A. M.:	No serum, temperature 99.8° F.	
	2.00 P. M.:	10 c.c., Type II, Banzhaf serum, 10,000 units	
	10.00 P. M.:	8 c.c., Type II, Banzhaf serum, 10,000 units	
February 6th,	10.50 A. M.:	10 c.c., Type II, Banzhaf serum, 10,000 units	
		Hemoglobin, 47.3 per cent.	
	6.30 P. M.:	10 c.c., Type II, Banzhaf serum, 10,000 units	
February 7th,	2.40 A. M.:	10 c.c., Type II, Banzhaf serum, 10,000 units	
		Hemoglobin, 45.5 per cent.	
	10.40 A. M.:	10 c.c., Type II, Banzhaf serum, 10,000 units	
	7.00 P. M.:	10 c.c., Type II, Banzhaf serum, 10,000 units	

February 9th, hemoglobin 42.4 per cent. temperature normal.

February 10th, pulse-rate 90, respirations 24.

On February 3d the patient received a polyvalent serum, and in the antibody detection test as described by Arlyle Noble and modified by Sutliff and Miss Cooper, we found he had an excess of I and III antibody, but not

of II. We interpreted this to indicate that as he was infected with a Type II, the Type II was neutralized and no excess was available. On this account on February 3d we increased the frequency and amount of the Type II serum. On February 4th we found the same condition, on February 5th, Types I and III. On February 6th the excess of I and II was eliminated because we had stopped giving him the polyvalent serum. He was getting a straight Type II, but had apparently not had enough.

His blood-culture tests were as follows:

January 30th, 24–32 per c.c.
January 31st, 9–0 " "
February 1st, 2–0 " "
February 2d, 7–2 " "
February 3d, 4–7 " "
February 4th, 9–14 " "

A series of protection tests, using the patient's own virulent culture, and the stock or RII culture (the same used in the making of the therapeutic sera), showed the following results:

February 2d, 1/50,000 of a protective unit, with the patient's culture, and 1/5 of a unit with the RII culture, both of which merely indicated a delay in death in the test, and not any actual units of protection. February 6th, the following were shown: 1/5000 of a protective unit with the patient's culture and 1/5 with the RII culture, merely indicating the beginning of a protection, not, however, sufficient to show in the blood-stream.

We continued the serum until February 9th when the patient's temperature fell to normal. During the illness of the patient, he developed a severe tracheobronchitis. On February 3d, he was less prostrate, although the fever was high and the pulse rapid. On February 6th, he was quite weak and unable to raise himself in bed. He was hoarse, but still did not seem quite as sick as on admission. On February 10th, the pulse-rate was 90, respirations 24, and the patient was much brighter. After this there was a steady improvement, and he was discharged from the hospital well, February 29th.

In several cases during the past winter, a severe tracheobronchitis has developed during convalescence, and in two of these it was found on inspection that secretion had dried on the walls of the trachea and larynx. In one, the dried secretion in the larynx proved to be an obstruction which actually interfered with the entrance of air. It is possible that the loss of water which accompanies the concentration in the blood may increase the formation of crusts.

Comment.—When the patient came into the hospital on the seventh day of his pneumonia, with a Type II positive blood-culture, he was markedly prostrated, and, according to our rating scheme, was in poor condition. We rate patients good above 70, fair between 50 to 70, and poor below 50. We have been unable to save any patients rated below 40. In our serum cases we have saved 63 per cent. of those rated poor, whereas we have saved none without serum. In spite of the very large doses of pneumococcus antibody, the patient's blood-culture continued positive, diminishing after the initial dose, but then began to increase.

A noteworthy discovery was made by the simple procedure of titrating the patient's serum for antibody content against Type II antigen. By this means, the fact was revealed that the Type II antibody had been completely combined with the specific soluble substance present in the blood-stream. At first the Type I and Type III antibodies administered were discoverable in the blood-stream, but later were found to have been excreted. It was possible to explain the persistent bacteremia and the failure to improve when we thus discovered that insufficient antibody had been given. Another cause of the failure with the dosage originally administered is probably to be found in the slight specific difference between the patient's own culture and the RII, as shown by the protection tests performed by Miss Alburta Brown. When we increased the doses of antibody, the blood-stream became sterile, and the patient improved. To prevent reinfection, the administration of serum was continued.

The modern treatment of pneumonia requires as much organization as the treatment of a patient suffering from a surgical condition, but the result is a reduction in mortality (as shown by our cases) of 42 per cent. in Type I and 22 per cent. in Type II cases, and a very definite shortening of the illness. This method of treating pneumonia requires more from the physician than the expectant method. It requires more equipment than a prescription pad and stethoscope, but the results are worth the effort. The literature contains no case of spontaneous recovery where there have been more than 30 colonies per cubic centimeter. In the present case, there were 24 and 32 colonies per cubic centimeter on admission.

A CASE OF PNEUMONIA OF TYPE X (MISCELLANEOUS GROUP)

E. M., aged twenty-five, residing in New York City, was born in North Carolina but had lived here for the past year. She entered the hospital June 19, 1928, with the following history:

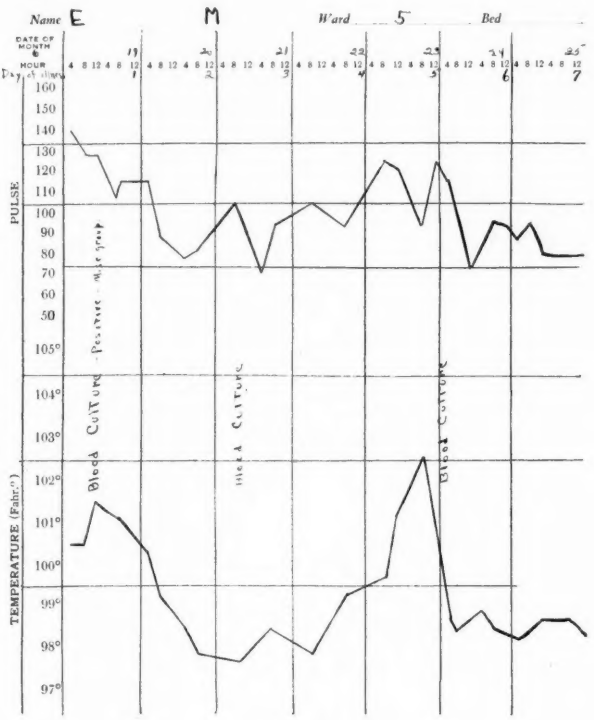

Fig. 131.

She was quite well until June 18th, 4 P. M. She then visited a friend with whom she had some whisky. A couple of hours later she started to feel the pain in the left side of her chest. The pain has increased in severity, and is

worse when the patient coughs. Cough began the morning of June 19th, and is productive of greenish-yellow mucus. She has had no hemoptysis and has vomited once on June 19th. Patient was caught in the rain several days previously.

Patient had influenza in 1917, takes alcohol, had frequent colds during the winter, often had spells of shortness of breath. Her menstrual periods started at fourteen, come every twenty-eight days, and last three days. She has had no period since August, 1927. She has had a white discharge before her periods.

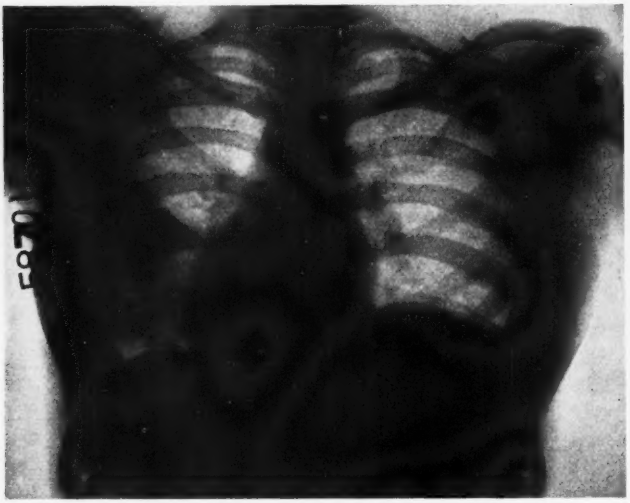

Fig. 132.—A pneumococcus pneumonia of Type x (Miscellaneous Group) involving the left lower lobe of which the physical signs were insufficient to establish the diagnosis, and the fluoroscopic evidence was equally inconclusive the preceding day.

Physical examination on admission was as follows: Patient is an adult colored female lying quietly in bed, breathing rather rapidly, and coughing intermittently, complaining of sudden pain in the left chest. There is a marked odor of alcohol on the patient's breath. She is fairly well developed and well nourished. The tongue is moist and tremulous. The signs over the lungs show dulness over the left lower lobe laterally. Throughout the whole chest are occasional sibilant râles, but there is no evidence of consolidation. The abdomen is slightly distended. There are ecchymoses over the right shoulder and arm. There are scars over the right wrist and left shoulder. A diagnosis of acute bronchitis with alcoholism was made on admission.

A fluoroscopic examination the next day showed a slight opacity in the left lower lobe. The signs were insufficient to make a diagnosis of pneumonia. She was not admitted to the pneumonia series, but a blood-culture was taken. *x*-Ray next day showed a clouding through the upper part of the left pulmonary field, due to consolidation, lobar pneumonia.

A blood-culture taken on the 19th showed a positive broth, and one colony on one of the agar plates. This proved to be a miscellaneous type of pneumococcus. The second blood-culture, June 21st, proved to be negative. Patient's Kahn test was 4+. Patient's rating was 48: Respiratory involvement 2, rate 5, apathy 5, circulatory rate 10, bacteremia 20, alcoholic 10.

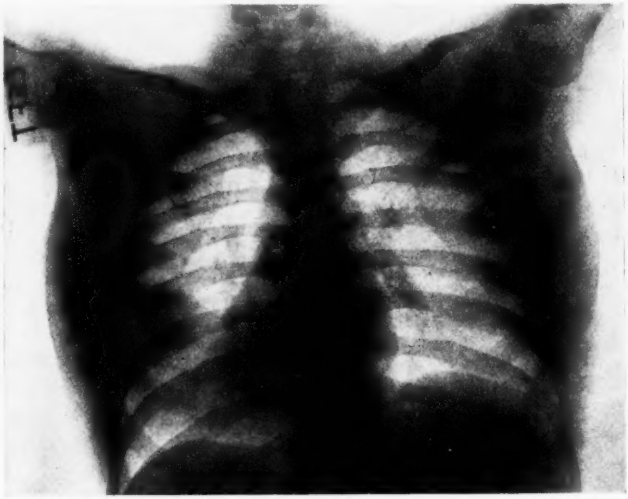

Fig. 133.—For descriptive legend see Fig. 132.

On June 21st in the left axilla in the third and fourth spaces bronchial voice and breath-sounds, and fine crepitant râles were present. The condition of the patient appeared remarkably good in view of the bacteremia.

The urine examination was negative. Blood-count: 10,500 white blood-cells, with 83 per cent., or 8715, polymorphonuclears, and 17 per cent., or 1785, lymphocytes. Red blood-count 4,000,000, hemoglobin 65 per cent., blood-pressure 80/40. Patient's temperature on admission was 101° F. It went up to 102° F. eight hours later. After this it ranged between 101.6° and 98° F., the highest temperature on June 21st being 99.2° F. The pulse continued relatively accelerated—90–106.

On June 21st, with the fall of temperature, patient became delirious, resistive, and somewhat combative. Her temperature rose to 103° F. on the 23d, and she had to be restrained. A blood-culture at this time was

negative. On the 24th her temperature and pulse fell rapidly to normal and she became mentally clear. From this time on, recovery was uneventful.

The interest of this case lies in the presence of a bacteremia in a patient, severely stricken, but with physical signs at first too slight to be definitely postulated without radiographic study. This patient was said to be suffering from pneumonia due to pneumococci of Type x (Miscellaneous Group).

Miss Georgia Cooper, working with Dr. Park in the Research Laboratory of the New York Department of Health, has, in the past season, by cross-agglutination and by protection tests with serum produced in rabbits, classified 55 per cent. of the miscellaneous group of pneumococci. This group was formerly called Group IV. She has classified this percentage into eleven fixed types. Some of these are very virulent. In each type the organism has been recovered from the blood of at least four patients suffering from pneumonia. Some of these types are less virulent. All of them produce antibody in rabbits, and one group (our present Type IV, not Group IV) is as large as Type III and has killed many of its victims, and produces in rabbits protective serum of strong titer. Horses have been vaccinated with these various types separately and in combination, and it is hoped that ultimately serum will be available which will save the lives of patients and shorten their illness. This has been demonstrated as possible for cases of Type I and Type II infections.

There was no incentive to subclassify the pneumonias induced by pneumococci of Group IV until this curative effect had been revealed, as the statistics reported in a paper by Park, Bullowa, and Rosenblüth, in the Journal of the American Medical Association, narrates. Miss Cooper has not thought it worth while to assign a number to any case in which an organism has been isolated in less than four cases, and on this account I have called this organism, tentatively, a Type x in the Miscellaneous Group.

When a pneumococcus occurs sufficiently frequently in a community, it is worth while to attempt immunization of horses for the production of therapeutic serum.

CLINIC OF DR. MILTON B. ROSENBLÜTH

FROM THE MEDICAL SERVICE OF HARLEM HOSPITAL, LITTAUER PNEUMONIA FUND OF NEW YORK UNIVERSITY

TREATMENT OF GROUP IV LOBAR PNEUMONIA

PNEUMONIA due to Group IV pneumococcus infection comprises a large proportion of all cases of this disease. In spite of the relatively low average virulence of this group of organisms it causes almost as many deaths as Type I and more than either Type II or Type III, the latter types being of lower incidence.

Because of their heterogeneous character Group IV cases are generally regarded as unsuitable for serum treatment, and it would appear most unlikely that any effective serum could be developed until the various strains comprised in this group are isolated. It has been suggested, however, that a polyvalent serum of the three fixed types be used in the treatment of the Group IV cases. The rationale of this procedure lies in the fact that an antipneumococcus serum of whatever type contains some antibody against other members of the species. It was hoped that even this small amount of protection might be a factor in saving some of these cases. Whether or not such advantage might accrue to these patients, and at this time the evidence is largely unfavorable to that view, the case which I am about to show will, I believe, make clear the advisability of so treating all Group IV cases.

The patient was a chauffeur, forty-four years of age. He was admitted on September 29, 1927, complaining of generalized chilly sensations and aching of his muscles and pain in right side of chest. He had a cough which was productive of a mucoid sputum without blood. His temperature on admission was 105.6° F., pulse 110. The physical examination showed signs of frank consolidation at the upper part of the right lower lobe. The leukocyte count was 11,200, polymorphonuclears 8064, monocytes 448, lympho-

cytes 2688, hemoglobin 90 per cent. The sputum was injected into a mouse and a Group IV pneumococcus recovered. Blood-culture taken on the day of admission showed 301 colonies per cubic centimeter; 7 c.c. of our antibody preparation No. 8 were administered intravenously at 3.30 P. M. on the day of admission. This contained 8000 units of Type I antibody, 660 Type II, and 1330 Type III. Eight hours later the same dose was repeated.

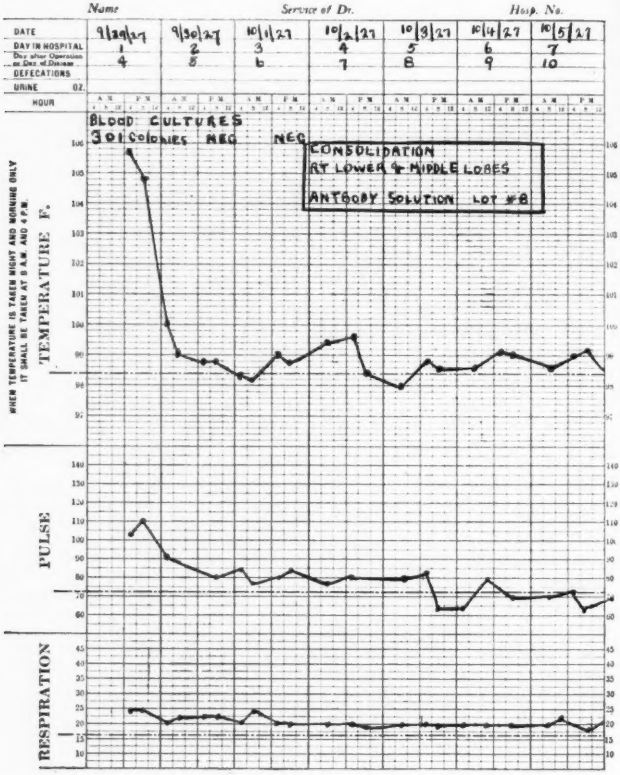

Fig. 134.

There was no reaction of any kind. The temperature dropped sharply from 105.6° to 99° F. and remained practically normal thereafter. A blood-culture taken on the second day in the hospital was negative. The effect of the serum in a case such as this with its marked bacteremia made it seem highly improbable that we were dealing with a genuine Group IV infection and

clinically we were impressed with the similarity of the response in this case to what we had become accustomed to see in Type I cases. On the second day of the patient's stay in the hospital a pneumococcus recovered from the heart s blood of the mouse which had been injected typed out as a typical Type I.

We have been unable to find in the literature any case with so marked a bacteremia which has recovered and we have reason to believe that without the use of serum this patient, too, would have died. The point which I wish to emphasize in this case is the importance of the treatment of all Group IV cases with a polyvalent serum because of the possibility that an error has been made in the typing. If this patient, because of the diagnosis of a Group IV pneumococcus, had been denied the use of the antibody solution we should have lost invaluable time before the correction in the typing was made.

Every effort is made by us to make our typings accurate and, particularly in Group IV cases, the results are always carefully checked; but the typing of pneumococci by all present methods is subject to a variety of errors in spite of prolonged experience and practice and the employment of elaborate methods. In this hospital our main reliance is upon the mouse method. Both agglutination and precipitation tests are carried out upon the peritoneal exudate. As a further precaution, the heart's blood of the mouse is cultured in order to obtain, if possible, a purer culture of the organism. If the sputum is suitable, that is, thick and abundant, the Krumwiede test is done and if only a small amount of sputum is available the Oliver test is used. In any case in which the organism is recovered by blood-culture, it is typed. The urine is examined for precipitins and, in a fairly large number of cases in which concentrated urine was employed, accurate typings were thus obtained.

Those cases which fall into Group IV or the miscellaneous group, as we prefer to call it, are subjected to special study in order to make certain that we are not dealing with one of the fixed types. Those cases which show precipitation and agglutination in all of the fixed sera are placed in Group IV. We have found, however, by making the tests with serum in serial

dilutions we were able to show that in some of the IV's the precipitation and agglutination were present only in the concentrated serum and disappeared as the dilution progressed; and that if it were actually a fixed type the agglutination and precipitation for that type persisted even in the very high dilutions. In this way we were able to change the diagnosis of Group IV to a fixed type in a significant proportion of cases.

To summarize then, a case of pneumonia has been shown in which a blood-culture taken on the fourth day of the disease showed 301 colonies per cubic centimeter. The pneumococcus recovered from the sputum was a Group IV organism. Administration of polyvalent antibody solution caused a critical drop in temperature within twelve hours and sterilized the blood. Subsequent study of the pneumococcus recovered from the heart's blood of the mouse proved it to be a Type I pneumococcus. The importance of treating all Group IV cases for at least forty-eight hours with antibody solution is stressed because of the possibility that the typing may be faulty and the pneumococcus may actually be of Type I or Type II.

CLINIC OF DRS. I. W. HELD AND
A. ALLEN GOLDBLOOM

BETH ISRAEL HOSPITAL

FUNDAMENTAL PRINCIPLES GOVERNING THE CLINICAL INTERPRETATION OF HEMATOLOGIC DISEASES

NOT long ago diseases of the blood-making organs were purely of academic interest, and a diagnosis of most of these conditions was the patient's death sentence. However, the advent of radium and *x*-ray treatment, as a means of prolonging the life of patients with chronic leukemia; of Katznelson's introduction of splenectomy in thrombocytopenia; and of the latest epoch-making therapeutic achievement of liver treatment in pernicious anemia by Minot and Murphy, have added practical interest to the study of hematology.

"Blood disease," a term erroneously employed to characterize conditions in which morphologic changes in the cellular elements of the blood occur, has continued in use because early research was directed chiefly to such changes. This research led to very important discoveries, namely, leukemia by Virchow, nucleated red blood-cells in the bone-marrow by Neumann, tinctorial methods by Ehrlich, and an elaboration of staining methods by Pappenheim. The contributions of Cabot, Drinker, Ewing, Howell, Minot, and others in this country, as well as in England, are also the result of close morphologic studies.

Drinker believes "blood disease" is justifiably applied to hematologic affections because, since the afflicted patient has no subjective symptoms directly pointing to the seat of his disease, diagnosis is based upon the morphologic changes of the blood. Such an argument might be applied to many diseases with resulting chemical changes in the blood, as, for

example, hyperbilirubinemia, where the patient's complaints need be directed neither to the liver nor to the destruction of red blood-cells, and yet we do not speak of these affections as "blood diseases."

Goldzieher reasons that, although the cellular constituents of the blood, an independent organ, are supplied by the hematopoietic organs, nevertheless, the cells encountered in these organs during postuterine life are not of the character of those contained in the blood, and that, because of this difference, the disease is rightfully called blood disease. An affection of the blood, however, does not manifest itself solely in changes in the blood's normal cellular elements. Hematopoietic organs resume their embryonic function and, as a result, the circulating blood-cells in the peripheral blood are identical in character to those encountered in the fetal hematopoietic organs.

In reality, the term "blood disease" originated when a symptom, especially a leading one, such as icterus, migraine, neuralgia, herpes zoster, and fever, was designated a disease. In the interest of diagnostic and therapeutic exactness, the name of a disease should be drawn from the organ causing the symptom, and, therefore, it is not surprising that the great clinician, Dr. H. V. Norrie, Bellevue Hospital, New York, and others are making an effort in the direction of clarifying medical nomenclature.

Like any other organ of the body (thyroid, heart, or kidneys) the hematopoietic system is subject to purely functional disturbances which give rise to subjective and objective symptoms without evident underlying pathologic changes. Outspoken morphologic changes in the blood may be encountered, and the condition is diagnosed blood disease clinically, but postmortem findings may reveal no pathologic changes in the hematopoietic organs macroscopically or microscopically. Morphologic changes in the blood do not indicate an organic disease of the system any more than, as is well known clinically, every case of oliguria or polyuria means kidney disease, or every case of cardiac murmur a myocardial or valvular affection. How often do we see cases at the bedside where differential diagnosis between

myeloblastic leukemia, thrombocytopenic purpura, or aplastic anemia is difficult! Even a careful search after death by a well-trained pathologist may fail to give a convincing decision.

The difference between functional and organic hematopoietic diseases lies mainly in the return of the hematopoietic organs to their embryonic function, and this may be laid down as a general principle. In organic hematopoietic diseases cellular changes in the peripheral blood generally indicate a disturbance in the hematopoietic system. Morphologic changes in the blood, if present at all, in functional disease, are slight and transient.

In postfetal life the bone-marrow, with its erythropoietic, myeloblastic, and megakaryocytic elements, and the hemolymph glands belong to the hematopoietic system. Should there be a disturbance of erythropoietic function, the resumption of embryonic function is evidenced by erythropoiesis. If the myeloblastic system is involved, pathologic variations are present in the white cells. If the megakaryocytic system is affected, the changes take place chiefly in the blood-platelets. The hemolymph glands are concerned with the production of lymphocytes. The gross appearance of the bone-marrow or the hemolymph glands, in an hematopoietic affection, depends upon which part of the system has resumed embryonic function.

PHYSIOLOGY OF THE CELLULAR ELEMENTS OF THE BLOOD

Red blood-cells originate in early fetal life from the walls of the primitive blood-vessels; late in fetal life from the liver and spleen. The liver loses its blood-forming quality early, but the spleen and lymph-glands retain it until toward the end of intra-uterine life, or soon afterward, when they assume the function of producing lymphocytes. Toward the end of intra-uterine life (until the age of sixteen) red blood-cells form exclusively in the bone-marrow. After that their formation is confined to the spongy flat bones and partly to the heads of the long bones, especially the femur and humerus. The marrow of the long bones until the age of sixteen, is red, after that, yellow. In affections of the erythropoietic system the bone-marrow is the first organ actually to show pathologic changes. All the

long bones, even in the shafts, resume their embryonic function, and the bone-marrow, losing its yellow color, because of the overproduction of red cells, turns red.

Large, nucleated red cells (megaloblasts) are present in the blood of the human embryo. The nucleus occupies the major part of the cell and the protoplasm is at first basophilic and polychromatic. Gradually the basophilic intensity increases, the nucleus becomes small and dense (picnotic), and the fine network disappears. The protoplasm now shows affinity for acid stains—a sign of full ripening—and this tendency toward normal staining is known as orthochromasia. When the nucleus disappears the megaloblast becomes the embryonic megalocyte. In late embryonic life, before the megaloblasts vanish entirely, nucleated cells called normoblasts (an unripe stage) are encountered. These are called microblasts by Naegeli, hemoblasts by Drinker. Pappenheim terms a still younger form "prolymphocytes." These contain no hemoglobin and may be detected in 1:300 aqueous solution of cresyl blue (Drinker's method) and are important when encountered in large numbers in severe anemia of childhood.

The denucleation of normoblasts is exactly that of myeloblasts, namely, karyolysis. The red cells increase, the nuclei disappear, and, although a large number of nucleated red cells, even macrocytes, may be present in the bone-marrow for several weeks in extra-uterine life, none reaches the circulation.

Extreme redness of the skin and marked capillary dilatation in early postuterine life are indications of a continued localized production of red blood-cells in the endothelium of the capillaries. *Ecchymotic areas and areas of yellowish discoloration are evidences of a mild localized destruction of these red cells.* Icterus neonatorum, it seems to us, indicates a severe degree of a local destruction of the red blood-cells in the endothelium of the skin capillaries, converting the hemoglobin into bilirubin. We know that there is no discoloration of the scleræ or fluid tissues in icterus neonatorum, and that the urine does not contain bile-pigments, although the stool is rich in them. It is unlike the rare form of icterus in infants, due to toxic hepatitis, or

congenital atresia of the bile-ducts, or icterus neonatorum gravis, with symptoms in the central nervous system, to which Greenwald and Messer have recently again called attention.

Red blood-cells contain salts, cholesterol, and lecithin, exerting an important influence upon the retention of hemoglobin in the cell membrane. The outer limiting membrane is of a homogeneous colloidal character, and prevents the passage of osmotic sodium chlorid up to 0.85 solution. When placed in concentrated solution it shrinks or, should the salt content decrease, swells until rupture occurs, allowing the hemoglobin to escape. This action, in hypertonic and hypotonic salt solutions, is known as the resistance of red blood-cells and is important, pathologically, as a diagnostic method. *The function of the red blood-cells is to carry oxygen and, to a lesser degree, carbon dioxid to the tissues.*

Leukocytes first appear in the circulating blood of the fetus as typical myeloblasts. They possess equally distributed protoplasm and nucleus, and are followed by myelocytes of a neutrophilic, basophilic, and eosinophilic nature, and, finally, by lymphocytes identical to those in the bone-marrow in postembryonic life. These myeloblasts and myelocytes disappear from the blood soon after embryonic life, although the latter are found in the bone-marrow throughout the whole of life. Lymphocytes are formed mainly in the liver, spleen, and hemolymph glands during intra-uterine life, and in the spleen as well as in the hemolymph glands, to a certain extent, during postembryonic life.

Leukocytes, in postembryonic life, number between 6000 and 8000, of which 72 per cent. are polymorphonuclears, 2 per cent. eosinophils, 20 per cent. small lymphocytes, 5 per cent. large lymphocytes, and 1 per cent. transitionals. Because of their phagocytic property, which is their main function, depending upon the alteration of viscosity, they have been intimately associated with ameboid movement. Polymorphonuclear leukocytes not only take up bacteria, but digest them readily through proteolytic ferments. Protease, lipase, amylase, maltase, and oxidase have been identified as endo-enzymes of the cells.

Blood-platelets, according to Wright, are derived from megakarocytes; according to Mall, they appear late in embryonic life; according to Brebichin, they come from osteoblasts. They are found in large numbers around the capillaries. The cytoplasms, by means of ameboid movements, find their way into the blood-vessels, and eventually work up into clumps of blood-platelets, likewise having ameboid movements. Blood-platelets are an indispensable factor in the coagulation of blood, according to present knowledge, and play a leading rôle in the formation of thrombi, supplying thromboplastin or thrombokinase. They are important in the erythropoietic process and in red blood-cell destruction, and number, normally, about 350,000 per cubic centimeter.

Endothelial Cells.—According to Naegeli, endothelial cells may be found in small numbers in normal blood due to trauma of the capillaries. This is important because, in many instances, their presence indicates definite pathology. A few may be found in the blood normally, oozing through the capillaries, and their presence does not necessarily indicate disease.

Reticulated Filaments (Substantia granulosa-filamentosa).—When hemoglobin is present in the red blood-cells, megaloblasts permit the occurrence of substantia granulosa-filamentosa, occupying, in the first stage, the entire cell, and lying radially in rosette and acorn formation around the nucleus. By cell division, these vital staining granules are arranged cross-like, around dotted nuclei and disappear with an increasing ripening of the erythrocytes. During the first days after birth they are plentiful, but subsequently disappear rapidly.

The torn part of the stroma is represented by vital staining, a representation of the ground structure of erythrocytes occurring only at the time of embryonic development, and in an affection of the hematopoietic system. Normally, the vital staining of the red cells is .1 to .2 per cent. of the total amount. An increase in the passage of vital staining granulocytic cells into the peripheral blood is a sign of increased erythropoiesis. These vital staining granules are present in practically 40 per cent. of all red cells in anemias, especially in those due to hemorrhage,

malaria, and bone-marrow carcinoma where bone-marrow function is active. The study of these elements has become very important because of liver treatment in pernicious anemia, and the staining method is, therefore, described:

A solution of cresyl blue is spread very thinly over a clean slide and heated over a flame to dry. A drop of blood is obtained in the ordinary manner upon a cover-slip which is immediately placed firmly upon the stained slide so as to mix the drop of blood thoroughly with stain. These reticulated cells stand out in contrast to the red blood-cells in that they stain blue in various forms, such as acorn reticulated filaments, etc., the number of reticulated cells per thousand red blood-cells will give the percentage, and the total is taken as compared to the total red blood-cell count.

Blut-stäubchen (Blood Dust).—In normal blood there is an element known as blood dust, regarded by many as a result of fat products because the quantity is considerably increased after a fatty meal. It may, however, consist of other substances, because some of it takes a basic stain.

NORMAL FUNCTION OF CELLULAR ELEMENTS OF BLOOD

Normally, red blood-cells vary little, numerically or morphologically. A temporary increase is present soon after intrauterine life. Epistaxis and hemoptysis are apt to occur upon changing from a low to a high altitude, due to the fact that the capillaries overfill with red cells and rupture under the strain. Even the lung epithelium may break down, as shown by Haldane. An almost acute polycythemia may be brought about by adrenalin injection, a rare condition in which a transient physiologic change occurs, attributable to a constriction of the capillaries, as was first experimentally demonstrated by Lanson. Mental excitement, due to suprarenal activities, and hot baths may produce a temporary polycythemia by dislodging red blood-cells from the liver into the peripheral circulation. A sudden or gradual obstruction of the portal circulation, as well as a slowly increasing obstruction of the pulmonary circulation (emphysema and arteriosclerosis of a pulmonary artery or

smaller vessel), will cause a permanent increase in the number of red blood-cells.

Leukocytes vary quantitatively during the course of the day. Ellerman and Erlandsen, quoted by Naegeli, found the following changes in a normal individual during one day, attributing them to cardiac activity: 6 A. M., 7400; 10 A. M., 8800; 3 P. M., 9200; and 7 P. M., 10,000. Active muscular exercise increases their number, explaining increased leukocytosis after exertion. Cold baths, too, cause an increase. Whether, normally, there is a physiologic digestive leukocytosis, is a moot question. Most observers find an increase after a heavy meal, and it was found in Pappenheim's laboratory that carbohydrates increase the number of lymphocytes; fat, the number of neutrophiles.

Leukocytes may be present to a considerable degree during the latter part of pregnancy and may number 20,000 during delivery and the first day of puerperium. This is important, because, should a patient run a temperature during the first day of puerperium, a high leukocyte count might be attributed wrongly to a severe infection or suppuration.

Doan and Zerfas[6] found that leukocytes in various diseases are subject not only to diurnal, but to wide hourly variations, the individual cells likewise being subject to numerical variations during the course of the day, phenomena ascribable to the fact that cells in the circulating blood are subject to a complexity of influences: Origin, maturation, delivery, longevity, destruction of the cell group, and variability of count. Doan and Zerfas also point out the existence of a striking reciprocity between myelocytes and mature polymorphonuclear leukocytes. Thus, the uniformity of maturation in the bone-marrow, and the periodicity of the fluctuations of neutrophiles in the peripheral blood, lead them to the hypothesis that there is a constant, functional withdrawal of granulocytes from the peripheral blood, and a periodic delivery of new cells from the bone-marrow, which, in leukopenia and leukocytosis, present a depression or stimulation, respectively, of the normal mechanism.

The cause of physiologic variation in the number of leuko-

cytes is frequently discussed, but this is definite: *The increase of white blood-cells physiologically does not depend upon an overproduction in the bone-marrow.*

Müller and Peterson have concluded that the numerical variation of leukocytes is influenced by the control of the vegetative nervous system over the innervation of the blood-vessels. They found, experimentally, that a diminution of leukocytes in the peripheral blood may be brought about suddenly by causing a parasympathicus reaction in the splanchnic vessels, or a sympathicus reaction in the blood-vessels of the skin, mature neutrophilic leukocytes gathering in the part of the vascular system where the parasympathicus influence predominates, in association with dilatation of the corresponding vessels. Müller showed, too, that a marked increase of leukocytes in the peripheral blood of a dog may be brought about by large doses of insulin without ensuing shock. Peterson noted that when peripheral leukocytosis occurs there is a hypoleukocytosis in the splanchnic vessels, and observed that an injection of peptone into dogs causes peripheral leukopenia and splanchnic leukocytosis, an effect the reverse of insulin injection, which causes peripheral leukocytosis and splanchnic leukopenia.

Many years ago Welch, of Baltimore, showed that an intravenous injection of dead bacteria into a rabbit decreases the polymorphonuclear leukocytes in the peripheral blood, and increases them in the splenic and hepatic parenchyma. Living bacteria injected directly into the liver and spleen cause an increase of leukocytes in these organs.

Winternitz showed that simple irritants will cause a mild local reaction, accompanied by a moderate leukocytosis. Strong irritants cause sterile pus with marked leukocytosis.

From the above it may be construed that red blood-cells and blood-platelets are more or less stationary, qualitatively and quantitatively, under physiologic conditions, but that leukocytes are subject not only to wide hourly numerical changes, but may alter, qualitatively and numerically, under physiologic conditions. At one time polymorphonuclear leukocytes predominate; at another, lymphocytes. The number of eosinophiles, too,

may vary and simulate an abnormal state. In parasitic diseases, bronchial asthma, colica mucosa, trichinosis, and after the subsidence of an acute infection, eosinophiles are frequently increased in number. Unripe leukocytes are often encountered in the circulating blood without any existing disturbance in the hematopoietic system, and polymorphonuclear cells may show a predominance of the non-segmented variety (staff cells), the so-called "shift to the left" of Arneth and Schilling.

Hematologic Diseases Affecting, Chiefly, the Erythropoietic System.—A disturbance of the erythropoietic system is evidenced in the bone-marrow and peripheral blood by a return of the hematopoietic organs to embryonic function. The bone-marrow overproduces red cells, again becomes red, and in it one finds large and small nucleated red cells in large numbers, macrocytes, microcytes, and practically all of the elements encountered in intrafetal life, depending upon the form and degree of anemia. Cabot's rings, Howell-Jolly bodies, blood-dust, and substantia granulosa-filamentosa may be found in the peripheral blood.

Now, according to most hematologists, the appearance of embryonic cellular elements in the peripheral blood is an indication of a regenerative process in the erythopoietic part of the bone-marrow. But the term "regeneration" is here illy applied. Ordinarily, it signifies a process in an organ that results in the formation of new tissue, later largely to replace normal function. We know that when the heart regenerates it resumes its function.

This, however, is not true of the regenerative process in the bone-marrow in affections of the hematopoietic system. Regeneration, in this instance, is merely a production of embryonic cells which not only do not ripen, but are subject to destruction unless the primary disease ceases, or, as pointed out by Sabin,[26] something is introduced from without, as liver diet in pernicious anemia, to enhance the maturity of the cell. We cannot say, obviously, that a nucleated red blood-cell is as efficient in carrying oxygen as the ripe, non-nucleated cell, that Howell-Jolly bodies, Cabot's rings, or blood-dust are as capable as normal

red blood-cells, or that we have in myeloblasts the immune bodies we have in normal leukocytes. If the production of unripe cells continues long enough, a watery-like aplasia of the bone-marrow eventually results, with almost complete absence of the cellular elements.

Therefore, we believe that regeneration is misleading, and that the term "reproduction"—referring not so much to a compensatory mechanism or to repair, as to a diseased mechanism producing unripe cells which are short lived and have a deleterious effect instead of functioning normally—is the one to which we should adhere.

Destruction goes hand in hand with disease of the erythropoietic system, and manifests itself by the following: Oligocythemia, microcytes, fragmented erythrocytes, and phagocytosis of the corpuscles by clasmatocytes, and deposits of iron pigment. Almost all forms of anemia are characterized by siderosis in the endothelial cells of the liver, spleen, and hemolymph glands. Another evidence of the destruction of red blood-cells is the presence of bile-pigments in the urine and blood-serum.

ANEMIAS

When an affection of the erythropoietic system takes place, the first clinical manifestation is anemia. As pointed out by the senior author in *Anemia—A Clinical and Hematologic Study*, published in the MEDICAL CLINICS OF NORTH AMERICA, January, 1927, anemia means, literally, a lack of blood, but is, in reality, a misnomer. There is not a lack of blood in affections of the erythropoietic system, but a lack of the cellular elements of the blood.

For the benefit of those who have not last year's publication before them, we take the liberty of reclassifying anemias as follows:

1. Anemias due to hemorrhage (acute and chronic).
2. Anemias due to carcinoma.
3. Infectious and parasitic anemias.
4. Alimentary anemia.

5. Direct diseases of the erythropoietic system:
   (*a*) Pernicious anemia.
   (*b*) Chlorosis.
   (*c*) Aplastic anemia.
   (*d*) Hemolytic icterus.
   (*e*) Sickle-cell anemia.
6. Anemia due to chronic interstitial nephritis.
7. Anemia due to lead and other chemical poisons.
8. Anemia of pregnancy and puerperium.
9. Anemia due to metabolic disturbances.

As the senior author's presentation last year dealt at length with the clinical and hematologic aspects of anemia, we shall abstain from repetition as much as possible, with the exception of emphasizing anemia due to carcinoma, pernicious anemia, and anemia due to puerperium, and shall concentrate, instead, upon points and affections not previously considered, with especial reference to differential diagnosis, mentioning illustrative cases that we have observed, and conclude with a discussion of treatment. To that end we are omitting a survey of alimentary anemia, chlorosis, aplastic anemia, hemolytic icterus, sickle-cell anemia, plasma-cell leukemia, and chloroma, and shall add only a few words to what was written earlier regarding anemia due to chronic hemorrhage, infectious and parasitic anemias, and anemia due to lead poison.

Anemia Due to Chronic Hemorrhage.—The hematologic changes in chronic bleeding (hemorrhage or oozing) depend upon the seat as well as cause of the bleeding. The reduction of hemoglobin is not as marked as in acute hemorrhage, nor is the reproductive process in the bone-marrow, although the bleeding has a stimulating effect upon it. It is a remarkable clinical fact that in certain anemias the reproduction phenomenon in the bone-marrow depends upon the seat of bleeding. Oozing from hemorrhoids, chronic duodenal ulcer, small polyps of the stomach or intestine, or uterine bleeding may give rise to such severe anemia as to simulate anemia due to carcinoma or pernicious anemia. On the other hand, a patient may have considerable bleeding from the lungs and chronic hemoptysis

without evidence of anemia. *Bleeding from an endothelial surface gives rise to less anemia than bleeding from a mucous membrane.* It is likely that reproduction in the bone-marrow is more stimulated when the bleeding comes from an endothelial surface than from a mucous membrane.

Anemia Due to Carcinoma.—Carcinoma ranks next to hemorrhage in frequency as a causative factor of anemia. From a clinical standpoint it may be divided into four types:

1. *Anemia due to the so-called cachectic carcinoma* is easily differentiated by the waxy white color of the face and the considerable loss of body weight, particularly of cutaneous fat. Hematologically, there is evidence of severe secondary anemia: absolute loss of rouleaux formation, and complete vacuolization of the blood-cells. Macrocytosis and poikilocytosis are more marked than anisocytosis. The blood-platelets are not markedly diminished, or, if so, only in proportion to the remainder of the cellular elements. There are no evidences in the peripheral blood of reproduction in the bone-marrow. The degree of anemia depends upon many factors, and, in all probability, the seat of the carcinoma plays a rôle.

In carcinoma of the cecum very frequently there is a slight involvement of the ileum and undoubtedly an abundance of bacteria exists in the cecum, which, through ileocecal valve incompetency, reach the ileum and so bring about the picture of severe anemia. The fact that anemia may be present with only a small carcinoma of the cecum close to the ileocecal region—not demonstrable even roentgenologically—is explained by the work of Seyderhelm,[29] who showed that by experimentally implanting cecal bacteria from the ileum of an animal a blood-picture similar to that of pernicious anemia might be produced.

2. *Anemia Due to Bleeding Carcinoma.*—The foregoing is the case, particularly if the bleeding carcinoma is of the gastro-intestinal tract, especially the stomach or rectum. Here the anemia is more marked than in a case of bleeding carcinoma of the lung, although the patient may have had hemoptysis or hemorrhage for a long time. In addition to the clinical and hematologic features mentioned above, leukocytosis (as in other

types of bleeding) and a diminution of blood-platelets are evident.

3. *In anemia due to carcinoma with bone-marrow metastasis* we may find striking evidence of reproduction in the bone-marrow. We may encounter nucleated red blood-cells and myeloblasts and myelocytes—in some cases as high as 10 or 12 per cent. When the primary seat of the cancer cannot be determined, one may be sorely pressed to differentiate the condition from secondary bone tumor, multiple myeloma, and subleukemic, myeloblastic, or myeloid leukemia.

4. *Anemia caused by carcinoma without bone metastatis, but with bone-marrow irritation*, may so mirror pernicious anemia as to make differential diagnosis impossible. Even on the post-mortem table the most trained pathologist may locate the primary seat of the carcinoma with the greatest difficulty. One is inclined to attribute this form of anemia to the toxic effects of carcinoma on the bone-marrow. That is why in this form of anemia, as in pernicious anemia, one encounters an excess of urobilogen and urobilin in the urine and an increased icterus index in the serum, indicating red blood-cell destruction. Here, too, one sees nucleated red blood-cells, polychromasia, and a moderately high color-index. Two features, however, differentiate it from pernicious anemia to a certain extent, and these are that there is not a predominance of macrocytosis and there is no megalocytosis. These patients respond transiently to transfusion. They are fairly well for several months and doubt may arise as to the diagnosis of carcinoma. If the seat of the carcinoma is removed after the tranfusion the patient may recover.

In one case we saw there was a carcinoma of the stomach no larger than a hazelnut. A most careful search revealed no metastasis, and yet, during life, the blood-picture was that of hyperchrome anemia with nucleated red blood-cells, macrocytes predominating. After death the bone-marrow of the long bones was wholly red, showing definite reproductive phenomena. In the majority of these cases there is no tendency to hemorrhagic diathesis, and, as a rule, there are no retinal hemorrhages,

serving to differentiate the condition from pernicious anemia. Neusser has stated that if the clinical is that of a first attack of pernicious anemia, without remission, and without evidence of retinal hemorrhages, a small carcinoma of the stomach should be thought of, and operation advised.

INFECTIOUS AND PARASITIC ANEMIAS

A form of anemia of great clinical importance, often deceiving the clinician, is due to bacterial or parasitic infection. In the severe type the anemia may be the only dominant symptom, and its cause, in the presence of negative blood-cultures, may not be demonstrable during life; perhaps not after death.

In severe streptococcic infections the hematopoietic organs may be affected to such a degree that blood disease is simulated. It is known, clinically, that streptococcic infection may take one of three routes: (*a*) In most cases it localizes in one or the other organs, causing suppuration; if it is accessible to surgical intervention, the condition becomes favorable for the patient; (*b*) the infection may cause localization in many organs, viz., the liver, kidney, or heart, leading to a fatal termination; (*c*) in some cases the streptococcic infection is so severe that the toxic effect upon the hematopoietic system is the most outspoken clinical picture. In such cases the clinical picture is of severe anemia with hemorrhagic diathesis simulating either subleukemic or aleukemic leukemia, or some severe acute infectious anemia. We believe that the severe types of agranulocytic anemia described by Schultze and Friedmann and the severe infectious anemia mentioned by Minot recently, and those described by Lederer are really cases of streptococcic infections. There are reports of agranulocytic angina where the blood-culture showed streptococci. Diagnosis is of the utmost importance, as in some of these cases—for instance, those of Lederer—blood transfusions have a beneficial therapeutic effect.

Severe anemia, particularly the subacute types, occurs in hematogenous infections of the kidney (the so-called furuncle of the kidney). In this disease the anemia may be the outstanding symptom with no complaint of pain over the kidney

region. If the infection is in the left kidney it may lead to a large tumor simulating a splenic enlargement, complicating the clinical diagnosis.

In a case seen by us, with Dr. Summer of Brooklyn—a male, aged twenty-one—there was a tumor mass in the left hypochondrium. Because of the severe anemia the hemic murmur of the heart, and temperature, the condition was diagnosed as subacute bacterial endocarditis. The tenderness over the tumor region would have suggested splenic infarction. In splenic infarctions in bacterial endocarditis crops of petechiæ will be found over various parts of the body, and in our case there were none. We suggested the possibility of a hematogenous kidney infection, and Dr. Fowler, of Brooklyn, after transfusing the patient, removed the left kidney and found it to be a sac of pus. The patient made a complete recovery.

In the Harmoriah Hospital some years ago a patient came in with a mass in the left side and with marked anemia, diagnosed as a splenomegalic form of anemia. After a careful study the conclusion was reached that the mass was due to a subphrenic abscess and the patient was operated on by Dr. A. V. Moschcowitz, after which he made a complete recovery. Several years later the same patient was seen by us with symptoms of penetrating duodenal ulcer, for which he was again referred to Dr. Moschcowitz, who operated upon him at Mt. Sinai Hospital. At this time Dr. Moschcowitz found, in addition to the duodenal ulcer, evidence of a healed, perforating lesser curvature ulcer which had most likely been responsible for the left-sided, subphrenic abscess.

A condition causing anemia with hematologic changes is that present in Streptococcus viridans endocarditis (called subacute bacterial endocarditis by Libman). The hematologic changes in the blood may be so outspoken as to simulate hematologic disease more than a chronic valvular Streptococcus viridans infection. Where the enlargement of the spleen is very marked some form of splenomegalic anemia, or even leukemia, may be suspected.

In 2 cases we had occasion to see, both clinically and on

the postmortem table, in the clinics of Professors Goldscheider and His of Berlin, the greatest difficulty in differential diagnosis was offered because of the presence of leukocytosis, and in one case 20 per cent. myelocytes. The final clinical diagnosis was subacute bacterial endocarditis which was confirmed by Professor Cellen at autopsy.

In the majority of cases of anemia associated with bacterial endocarditis the clinical picture is so evident that a differential diagnosis is not very difficult. Regarding the hematologic picture, in addition to the signs of secondary enemia, there is usually a leukopenia with staff cells predominating. Not infrequently endothelial cells are encountered in the blood. This was recently brought to our attention again by Dr. Rosenthal of Mt. Sinai Hospital. Whether this is due to a special form of immunity these endothelial cells possess against this infection—as asserted by Libman—or whether *it is a primary weakening of the capillaries, allowing the endothelial cells to get into the circulating blood* (which we believe it to be) cannot be definitely decided. In view of the fact that the endothelial cells present in this infection appear in only that form of bacterial endocarditis where the embolic phenomena predominate, it would seem to indicate that the weakened state of the capillaries is the more probable explanation. In reality, hematologists long ago pointed out that under conditions where there is a weakened wall of the capillaries, as, for instance, in hemophilia or purpura, endothelial cells may be encountered in the blood. This would show that these cells have nothing to do with immuntity to bacterial disease.

Schottmüller called attention to the fact that chronic Streptococcus viridans infection of the gall-bladder (cholecystitis lenta) may lead to a form of chronic sepsis and anemia. This is a very rare disease, but it has been confirmed. Recently Dr. Klemperer, of Mt. Sinai Hospital, at one of his postmortem conferences, showed an instance of Streptococcus viridans infection of the gall-bladder and large bile-ducts that led to a general chronic sepsis and a fatal termination.

Prostatic, perinephritic, subphrenic, or pulmonary abscess, infection of the sinuses, teeth, etc., are among the chronic bac-

terial infections. Just as the degree of anemia is determined by the source of bleeding in chronic oozing hemorrhage, so in a chronic infection of an endothelial surface the degree of anemia is greater than in a mucous membrane infection. A prostatic abscess, or a chronic pulmonary suppuration, or even pulmonary gangrene, does not cause as marked anemia as a paranephritic abscess invading the capsule of the kidney, or a liver abscess invading the capsule of Glisson, or even a localized abscess reaching the pleura.

In acute syphilis, a spirochetal disease, temperature, enlargement of all the glands, and anemia may be present, simulating a hematologic disease, but the diagnosis in these acute cases can be readily established by the Wassermann test, which is positive in 100 per cent. of these cases. Anemia in syphilis may sometimes be confused with Banti's disease. Achylia gastrica, with or without anemia, may occur in syphilis even before tabes sets in. During the chronic stage of syphilis enlargement of the spleen and liver with anemia may give rise to the clinical picture of Banti. The diagnosis is especially difficult if the history of syphilis is denied by the patient or if the patient does not know he has contracted syphilis, and should the Wassermann test be negative. Sometimes anemia and achylia gastrica are present in syphilis and suggest the possibility of pernicious anemia. It has long been known, and was especially pointed out by Brugsch and Schneider, that achylia gastrica is frequently associated with syphilis. In fact, they called the condition syphilitic gastritis. They state correctly that it is a part of syphilis of the other viscera, and a forerunner of tabes dorsalis. It is well known, of course, that a picture fully that of a pernicious anemia may be caused by syphilis. Whether pernicious anemia is a co-affection or is actually caused by syphilis is a matter of conjecture.

Malaria follows next in importance as a cause of anemia. A badly, or insufficiently treated malaria, gives rise to anemia of the secondary type. Such patients may run only a subfebrile course, a result caused by the anemia and not by the malarial parasite. Ordinary examination of the blood may not reveal

the actual cause, and the splenic enlargement, the leukopenia, and the mononucleosis may lead us to a wrong diagnosis of Banti's disease. It is essential in these cases to use methods that will help bring the malarial parasite into the blood, as, for example, the subcutaneous injection of 1 c.c. of adrenalin, or the application of heat over the spleen. In acute malarial infections, especially those due to the tertiary type, erythrocytes may be seen in the circulating blood during all stages. Nucleated red blood-cells, poikilocytosis, anisocytosis, microcytosis, and often megaloblasts may be encountered.

During relapses of chronic malaria the blood-picture of severe anemia, with the presence of parasites, may exist. In the severest form the picture of aplastic anemia may be present with aplasia of the bone-marrow, differing during life from true aplastic anemia only by the absence of hemorrhages. It is important to remember that although the blood-platelets in malaria are diminished, there is no hemorrhagic diathesis. Some describe a diminution of specific gravity as characteristic of malarial blood. Cabot's rings and Howell-Jolly bodies may be encountered, and basophilic granules are always present in the red blood-cells. There is usually leukopenia, with predominating mononucleosis and, at times, a lymphocytosis. In addition to the splenic enlargement there is a considerable enlargement of the liver in severe cases, thus complicating the clinical picture. The severest type is characterized by a marked destruction of red blood-cells, leading to blackwater fever. A thorough study of the blood will reveal certain characteristics of malaria. The red cells are larger than normal and stain poorly. They show the so-called Schüffner dipplings—small dots that are round at first, then spread equally over the entire blood-cells. They stain intensely red with chromatin. In the tertiary type of malaria, coarse granules, known as Brug's spots, are seen, in addition to the Schüffner dipplings.

PERNICIOUS ANEMIA

Since Minot and Murphy[16, 17, 18] clinically confirmed the discovery of liver feeding as a therapeutic agency (one of the

greatest therapeutic achievements in the history of medicine) the diagnosis of pernicious anemia is no longer academic, but vitally important. The studies of Minot and Murphy have stimulated research as to the etiology of pernicious anemia, and many theories, such as the toxic, vitamin, avitaminosis, an increase of unsaturated fatty acid, and internal secretory disturbances, have been offered. None has as yet been sufficiently established to warrant definite conclusions.

Jungmann[14] adheres to the opinion that pernicious anemia is due, primarily, to an increased destruction of red blood-cells caused by a vitamin disturbance. He bases his conclusion on the fact that, with improvement by liver extract, the urobilin and urobilogen disappear from the urine.

Minot, Murphy, and their co-workers[19, 20] deny the importance of blood destruction and vitamin disturbance as causative factors in pernicious anemia. According to them, the lack of maturation of the red cells is primarily the cause of pernicious anemia, and, to prove the contention, point out that with the improvement of pernicious anemia the reticulocytes in the blood increase considerably and the maturation effect on the red cells is evidenced by their quick return to normal shape and hemoglobin content. According to them, the white cells, too, show an increased maturation tendency. Sabin,[26] also, upholds the maturation theory.

It seems to us that the controversy between those who believe pernicious anemia due to blood destruction and those who believe it due to lack of maturation is an artificial one. One has still to find out why maturation is prevented, predisposing red cells to early destruction. *The actual typical picture of pernicious anemia may be due to several causes, both factors mentioned contributing.* However, the true Addison type seems to us best explained on the basis of some constitutional inferiority of the erythropoietic system, consisting mainly in an *endogenous* vitamin disturbance which may have the effect, as stated by Minot, Murphy, and Sabin, of preventing the red cells from maturing, or exposing them to early destruction. We are inclined to believe that many affections, characterized by dis-

turbance in the hematopoietic system and by hemorrhagic diathesis, have their explanation in an obscure endogenous vitamin disturbance, as scurvy has such a cause, and hemophilia, the most successful treatment of which, as shown by recent studies of Spanish investigators, reported by Nieukau,[24] is by a combination of the A, B, C, and D vitamins. Although there is as yet no experimental proof, this may be the explanation of why the liver and kidney diet is beneficial in pernicious and not in other anemias. *It is possible that in pernicious anemia the liver or kidney substance mobilizes the vitamins in the erythropoietic system, allowing the products (red cells) to become mature, and thereby preventing their destruction.* It is possible, also, that this vitamin disturbance has a deleterious effect on the reticuloendothelial cells of the spleen, causing destruction of the red blood-cells. Since the studies of Eppinger in 1912 and 1913 splenectomy, in certain instances, has had a transient favorable effect upon the blood-picture of pernicious anemia. The constitutional factor is borne out by the familial character of the disease. Although it does not characterize it as frequently as it does hemolytic icterus, nevertheless, it deserves attention. The constitutional factor would explain, too, why identical etiologic factors may produce the disease in certain individuals, and not in others.

Of late, a great deal of attention has been given in the clinic to the external appearance of a patient as an indication of constitutional inferiority. Draper[8] has described special constitutional types afflicted with pernicious anemia. It has long been known that those who become prematurely gray are more subject to it than others. In fact, Neusser used to say that he had never encountered pernicious anemia in a black-haired person. This is not accepted by all clinicians, some believing that pernicious anemia comes first and after that gray hair. It has been said, too, that stocky, broad individuals are more prone to the disease. Draper found that individuals afflicted with pernicious anemia have short, broad facies, large mandibular angles, very short noses, short but deep, wide chests, especially wide subcostal angles, and the males have very long, thin ears. He

states that the male of the pernicious anemia race is a medium to tall individual, with a short chest, high-placed umbilicus, long abdomen, and a tendency to eunuchoidal habitus as shown by the relatively long lower extremities. They show definite effeminate tendencies in the domain of secondary sex characteristics.

Lichty, in this country, and the late Pappenheim, abroad, stated that the fact that certain mild cases of anemia eventually drift into the picture of pernicious anemia is proof of the constitutional basis of the affection. Barker has recently considered it an hereditary fact, putting forth the concept that it is a genotype disease, possibly only a biotype, requiring certain releasing factors in the environment for its development.

The relationship of achylia gastrica to pernicious anemia is a much discussed question. Knude Faber and many others believe it a primary cause of pernicious anemia, and practically always present in this disease. We agree that, in the absence of achylia gastrica, it is very daring to diagnose pernicous anemia. According to some statistics there may be free acid in the gastric contents in 2 per cent. of the cases of pernicious anemia. Since subtotal gastrectomy has been practised for gastric and duodenal ulcer, having as its accomplished object the production of achylia, some cases of pernicious anemia following it have been reported. Hartmann, of the Mayo Clinic, reports a case, a patient fifty-eight years of age, who had a subtotal gastrectomy for carcinoma of the stomach. The patient did well for one year, and developed a typical picture of pernicious anemia. Hurst, in London, states that he saw, in Vienna, 3 cases of pernicious anemia following subtotal gastrectomy for carcinoma. One must conclude, however, in view of the fact that only a small number of individuals develop pernicious anemia after induced achylia (following subtotal gastrectomy), there must have been a constitutional defect in these individuals, favoring the development of an affection which would have occurred without an operation, and which might only have been hastened by the induced achylia.

Symptoms of Pernicious Anemia.—Before describing the symptoms of pernicious anemia, it is timely to discuss the term. It

is one which, since Minot and Murphy's[16, 17, 18] specific treatment of pernicious anemia, should be discontinued. Even before, it was unfair because it was so alarming to the patient. The outcome of the disease may have warranted a term that was cruel, but, however that may be, today it is unjustifiable. Schilling[27] proposes hyperchromic megaloblastic anemia as a substitute. This is very good, but as it adheres only to the most characteristic hematologic findings, and as these need not be present in all cases, it leads to confusion. We feel it should almost invariably be called Addison's anemia, or, if tradition be truly adhered to, there is more reason than ever to call it Addison-Biermer anemia.

The first symytom of outstanding importance is the facies, that of a sallow, yellowish-pale individual, with an occasional icteroid tinge, but without icteric discoloration of the sclera. The face is puffed and, as a rule, there is no evidence of loss of body weight. In fact, the panniculus adiposis is well retained and makes the overlying skin very tense, and unlike the flabby, wrinkled, and easily lifted skin of other forms of anemia. There is another facies recently described by Naegeli. Although evidencing extreme despondence and sadness, it does not disclose real suffering. Neusser was wont to say that a patient with pernicious anemia never smiles during the active stage, but appears hopeless, without expressing his feeling in words. In anemias due to other causes the patient, during the period of improvement of his subjective symptoms, assumes a hopeful attitude, resuming an active interest in his environment. Today, the first sign of improvement during a natural remission of pernicious anemia, or one following a successful liver treatment, is the smile on the face of the patient as he greets his physician. This is so characteristic that it cannot be overemphasized.

Another notable subjective symptom is the extreme weakness, most likely responsible for the despondent facies and cessation of interest. During the active stage of pernicious anemia, except in carcinomatous cases where it may be increased, sex libido is lost, contrasting with anemia due to other causes where, unless the condition is markedly advanced and

if the patient is free of subjective symptoms, sex desire is unaffected. If the patient has enough physical rest it may even be normal. Extreme loss of appetite is another subjective symptom of pernicious anemia, and occasionally there may be a perverted appetite, the patient craving sour and spicy foods. In spite of the low blood-cell count and low hemoglobin, the patient has no dyspnea for the reason that there is more hemoglobin to each red cell. Unlike other anemias—particularly those resulting from hemorrhage—the patient has no tendency to fainting spells. Hemorrhagic diathesis is not the rule, despite the considerable lowering of blood-platelets. At times, particularly in severe cases, there may be petechiæ on the palate, and perhaps ecchymotic areas over the skin. Retinal hemorrhages are not uncommon, and help in diagnosis.

Prior to the introduction of liver treatment the progress of the disease was divided into three periods. The first was characterized by the fact that, although the symptoms as well as the blood-picture were very pronounced, and blood crises might occur with a hemoglobin as low as 25 per cent., and a red count of less than 1,000,000, nucleated red blood-cells of the megaloblastic type being present in the peripheral blood, all cellular structures indicated a reproductive process in the bone-marrow, and, occasionally, the patient would begin to improve without transfusion, and would recover in a few weeks. Later there would be a second period, during which the symptoms recurred, and, although not as severe as during the first attack, the disease would progress gradually, notwithstanding treatment, to a fatal termination. In some instances the second period would be interrupted by a remission, and, after a number of months, a third relapse would occur, and, within a short time, prove fatal. These stages were so representative that the clinician, Friedrich Kraus, of Berlin, used to say: For the first period, every physician is good; for the second, the family of the patient begins to doubt the doctor's ability; and by the time the third attack sets in no physician is good enough. Of course, under the present method of liver treatment, we hope the great majority of pernicious anemia cases will no longer be subject to these divisions.

Gastro-intestinal Objective Findings.—1. *Hunter's glossitis* is present, according to some authors, in 100 per cent. of the cases at one time or another. It is recognized by burning of the tongue and the presence of small vesicles with a red zone around the edges, and occasionally on top of the tongue. It may occur periodically, and may precede the true clinical picture of pernicious anemia. Some of the papillæ on the surface of the tongue, particularly in the back, are characteristic. Similar lesions may spread to the esophagus and the rest of the gastro-intestinal tract, giving rise to severe burning in the epigastrium and substernal regions. Although this cannot be demonstrated during life, it must be considered, particularly when the patient complains of burning in the epigastrium.

2. *Diarrhea*, without much pain, mucus, or blood in the stool, in the presence of anemia, should awaken suspicion. The stool rarely contains undigested food particles, and is, therefore, unlike that of pancreatic and gastrogenic diarrhea. It is rich in bacterial flora. Anemia with diarrhea, not associated with rectal tenesmus or intestinal cramps, according to Neusser, should exclude the gastro-intestinal forms and make one think of pernicious anemia, even without the characteristic blood findings. It seems the diarrhea is purely neurogenic.

At times the anemia caused by carcinoma of the stomach may be so difficult to differentiate that a complete *x*-ray series of the gastro-intestinal tract must be resorted to in order to rule out carcinoma of the stomach or colon. And, in spite of all aids to diagnosis, autopsy will prove us wrong when we least expect it.

Sensory Gastro-intestinal Symptoms.—1. *Pain in the upper abdomen* may be so severe as to suggest carcinoma of the stomach, or, in view of the severe anemia, a bleeding ulcer. The pain may remain unrelieved unless the hematologic symptoms improve. It cannot be attributed to achylia gastrica analogous to achylia gastrica dolorosa because, if so, it would be present in more cases of pernicious anemia. Recently we saw a case where the pain was so intense that, although the patient had outstanding symptoms of combined sclerosis of the cord, she was operated upon in the belief that a surgical abdominal con-

dition existed. The cord symptoms in her case were due to pernicious anemia, and improved considerably under liver treatment. This pain may give rise to severe colic and may be present without considerable anemia. Only recently Eppinger and Matanson mentioned and reported several cases, calling the attack "pseudogall-stone colic." It is important to remember that this condition does occur, and that in the presence of only slight anemia pernicious anemia must be thought of. It is due, probably, to excessive destruction of the blood, an overproduction of bile-pigments which may cause actual biliary obstruction, and a resultant alteration of the bile constituency. This colic is not as frequent in pernicious anemia as in hemolytic icterus. If, in the course of pernicous anemia, an attack of such a colic shows an increase not only of the indirect but the direct bilirubin in the serum, and if the urine contains considerable bile (bilirubin) in addition to the urobilin, a diagnosis of obstructive calculus jaundice is justified.

2. *Thoracic pains*, even of the severity characteristic of stenocardia, may be present in pernicious anemia. Many authors, notably Herrick in this country, believe that stenocardia is a rather frequent accompaniment of pernicious anemia. It is probable that such patients are afflicted with coronary disease as well as pernicious anemia. Precordial pain, not absolutely typical of stenocardia, is present in many patients with pernicious anemia, and is due, most likely, to the cardiac ischemia.

3. *Dysphagia* in pernicious anemia has been described again by Jones and Owen recently. They mention cases where dysphagia simulating carcinoma of the esophagus was encountered, and where a most careful examination during life, including esophagoscopy, as well as a postmortem examination, failed to reveal any malignancy of the esophagus.

Not long ago we encountered 2 cases with a blood-picture of pernicious anemia with no dysphagia present. At a subsequent examination of the gastro-intestinal tract *carcinoma of the lower third of the esophagus was encountered.* This is mentioned to illustrate the difficulties one encounters in the clinic. The cases of Jones and Owen presented clinical symptoms of

carcinoma of the esophagus without the presence of carcinoma, whereas our cases had no symptoms pointing to carcinoma of the esophagus, but had a blood-picture of pernicious anemia.

Neurologic symptoms of pernicious anemia are of great importance. They may vary from slight paresthesia to outspoken symptoms due to subacute combined sclerosis of the cord. There is usually a spastic gait with the presence of Babinski, Oppenheim, Gordon, and increased clonus. In some cases the posterior cord involvements are more marked, giving rise to the symptoms of a tabetic cord lesion. It must be remembered that such cord symptoms as combined sclerosis may be present in a pernicious anemia complex, due to a carcinoma of the stomach or colon, without any metastasis to the spinal cord.

Febrile Reactions.—Some patients may run a temperature for weeks, complicating differential diagnosis.

Splenic enlargement is usually found at postmortem examinations of pernicious anemia patients. At times the spleen may be as large as in Gaucher's disease, thereby complicating differential diagnosis, as in a case we recently encountered. Again, it may not be detectable on physical examination, but the absence of a palpable spleen does not speak against a diagnosis of pernicious anemia. The liver may be enlarged clinically.

Hematologic Picture.—In the words of Pappenheim, although the blood-picture of pernicious anemia is more or less characteristic, it is by no means conclusive. The positive findings should guide us and justify our diagnosis. There is a high color index and there is an increase in the size of the red blood-cells. There may be macrocytosis, even megalocytosis. Nucleated red blood-cells are usually present in small numbers and are generally large—macroblasts, rarely megaloblasts. There is generally a diminution of the reticulogranulofilamentosa of the blood as well as of the blood-platelets. The cause of hemorrhagic diathesis lies in the diminution of blood-platelets. Hypochromasia and polychromasia are present. There is almost a complete loss of chrome in the red cells, a disturbance in rouleaux formation, extreme poikilocytosis and anisocytosis, with Cabot's rings, Howell-Jolly bodies, and occasionally blood-dust. As to white

cells, leukopenia is the rule. According to Zadek and Arneth, there is a tendency to deviation to the right, namely, the dominance of a polymorphonuclear segment. Zadek points out that

Fig. 135.—Erythrokonten in basophilic punctated erythrocytes (macrocytes). Giemsa stain.

leukocytosis in the course of pernicious anemia is of bad prognosis. This is not agreed upon by all authors.

V. Schilling[27] points out that erythrokonten are characteristic in pernicious anemia, although found occasionally in other

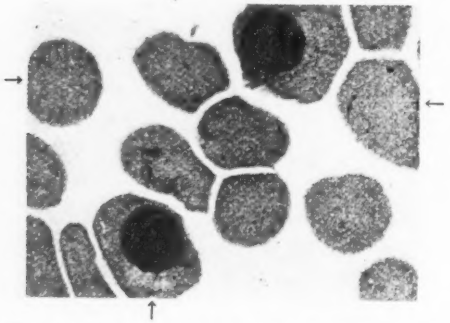

Fig. 136.—Bartonellen in each single erythrocyte.

forms of severe anemias. They are rod shaped or bacilli shaped, sometimes they are curved with thick ends, and lie mostly in the red cell proper, especially in the megalocytes. Occasionally, they lie outside the cell and resemble remnants of cells or bac-

teria, but Schilling states definitely they are not bacteria. They also resemble contaminated stain particles, and are found in small numbers, sometimes one in a field, which he terms +1, as shown in Fig. 135. Sometimes two or three are found in a field, when he speaks of them as + + (Figs. 136, 137*). Again, many are found (Fig. 138). They cannot be seen with ordinary stain, but only by the thick drop method on a very dry slide from which the fat has been thoroughly removed. The method of Schilling must be strictly adhered to in order to obtain results. We call attention to it because the information comes from an important, careful observer, and deserves to be followed up.

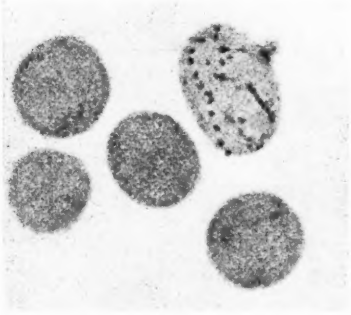

Fig. 137.—Erythrokonten in basophilic punctated megalocytes pernicious anemia: Nile-blue-sulphate chamber staining.

We are at present employing his method as follows: (1) The slide must be fat free; (2) we spread the slide with 0.5 per cent. Nile-blue-sulphate solution and absolute alcohol; (3) we spread the blood in the usual way on the stained dried slide. Before the slide is dry we place it in a moist chamber (Petri dish) for 3–5 min.; remove; allow to dry in air.

Of outstanding importance, as pointed out recently by Nellis B. Foster and his associate, Alice Bernheim, are the increase of icterus index in the blood-serum, and the marked increase of urobilin in the urine. The serum is usually dark yellow. These

* Illustrations after V. Schilling, Klinische Woch., 7th Year, No. 17, April 22, 1928, p. 785.

are absolute evidences of red cell destruction and incline us to the conception that pernicious anemia is due mainly to red cell destruction rather than to a lack of production. The deleterious effect, as asserted by Eppinger, must lie in the spleen.

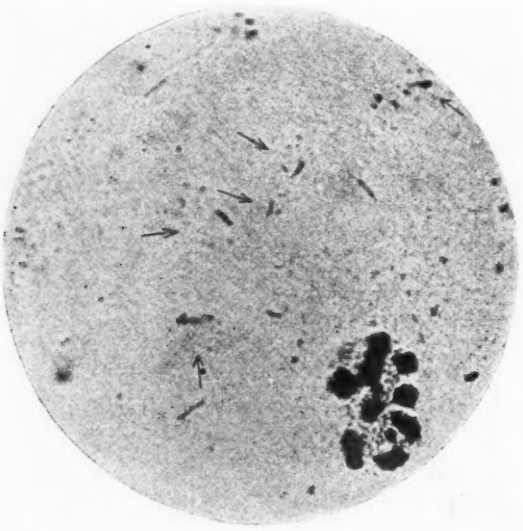

Fig. 138.—Erythrokonten in thick drop method. Nine small rods, three long and sharp rods, visible (at 1, 5, 8 P. M.), etc.

When the above findings are present, one may be fairly certain he is dealing with pernicious anemia.

ANEMIA DUE TO LEAD OR OTHER CHEMICAL POISONS

Because of the importance of basophilic granules (reproductive forms of erythrocytes) in the diagnosis of lead poisoning, we present an exact staining method not included in the paper of last year:

The slide must be thoroughly cleansed with alcohol in order to remove any fatty substance. A blood-smear is made and allowed to harden for three minutes in methyl alcohol. If it hardens while the slide is wet, it is placed in dilute Loeffler methylene-blue solution (1 part solution to 8 parts water), after

which it is washed in water and dried. The erythrocytes are stained green, the granules deep blue. At times the granules are so numerous as to cover the entire erythrocyte. Occasionally, in lead poisoning, one encounters polychromasia as well as a relative lymphocytosis.

ANEMIAS OF PREGNANCY AND PUERPERIUM

Osler's classification of these anemias is:

(1) Those secondary to postpartum hemorrhage.

(2) Severe anemia of pregnancy showing forms of secondary, pernicious, or aplastic anemia.

(3) Postpartum.

(4) Acute, as a result of puerperal sepsis.

Clinically, the classification is good. Practically, its chief interest is where the cause cannot be traced. One may find the characteristics of either marked or aplastic anemia, with a favorable termination, and, in many cases of anemia following puerperium, complete recovery does take place, although in some instances the anemia recurs with succeeding pregnancies. Repeated transfusions have a favorable influence.

Many theories have been advanced for these anemias. None has been substantiated. Hoefbauer believes that hemolysis is produced in the ectodermal cells of the chorion "syncytium." When encountered, the anemia is usually early in pregnancy, because the hemolysis disappears later with antihemolysis. If antibodies fail to form, a destructive anemia tends to result. Calloup and O'Hara assert that parturition may interfere with blood-forming tissue due to a substance produced from the fetus. Progressive anemia might result if the hematopoietic mechanism failed to compensate. McQuareine thinks all are toxemias of pregnancy.

ANEMIA DUE TO METABOLIC AND INTERNAL SECRETORY DISTURBANCES

Severe diabetics may occasionally present the clinical picture of marked secondary anemia. So also may patients with chronic joint affections. Of the internal secretory anemias, myxedema

is chief, with anemia, perhaps, the most outspoken symptom. Cases of myxedema simulating pernicious anemia have been described. Again, there is Addison's disease, where, if the brown discoloration is not marked, the condition may resemble pernicious anemia.

Addison's disease and pernicious anemia are clinically and etiologically different, although they may possess certain symptoms in common. An individual afflicted with Addison's disease almost invariably loses weight rapidly. Asthenia is the most marked symptom. Nearly all patients with Addison's disease, even when it is not far advanced, are almost continually confined to bed, and the sudden death in Addison's disease is that of pure asthenia. The blood-pressure in pernicious anemia, although generally low, is never as low as in Addison's disease. Really, if arteriosclerotic changes are present in pernicious anemia, the blood-pressure may be high, a condition never encountered in Addison's disease. Although both affections may have pigmentation of the skin over certain parts of the body, the pigmentation in pernicious anemia is never as diffuse as it may be in Addison's disease, and it is never present in the mucous membrane of the mouth.

POLYCYTHEMIA

The clinical entities so far discussed have been affections of erythropoiesis in which there is a reduction of hemoglobin and red blood-cells. Polycythemia is a disturbance of the erythropoietic system in which there is an increase of red blood-cells and hemoglobin. There are various symptomatic forms of polycythemia, such as those due to hyperventilation in the course of chronic emphysema and congenital heart disease, particularly of pulmonary tuberculosis, or of poisoning with carbon monoxid, and the so-called Ayerza disease (chronic cyanosis and splenic enlargement). These secondary symptomatic polycythemias have nothing to do with primary disturbances of erythropoiesis.

Two types of polycythemia vera are usually described: The Osler-Vaquez, splenic enlargement without blood-pressure

changes, and the Geisbock type, without splenic enlargement and with an increase of blood-pressure. Numerous theories of the etiology of this disease have been advanced, one school asserting that there is a failure of destruction of the red blood-cells; another, overproduction. The failure of the spleen to destroy red blood-cells (hyposplenia of Eppinger) is the more plausible theory and is substantiated by the fact that even a normal trace of urobilin is absent from the urine in this disease, and that the icterus index, as well as bilirubin in the serum, are considerably below normal. It is interesting that a lack of destruction of red blood-cells may at times change into overproduction, and the condition may eventually be converted into pernicious anemia. Instances of this, as well as of a development of leukemia in polycythemia, have been reported—additional evidence of the interrelationship of the hematopoietic organs and the co-affection of one system by the other.

Clinically, the chief characteristic features of polycythemia are the cherry-red face, conjunctiva, hands, and feet. The hands and feet feel hot to the touch, and many observers have noted an increase of body surface temperature compared to healthy skin. It has been found, too, that the skin temperature is higher over the cherry-red areas than over other parts of the body. Itching of the lower extremities, caused, probably, by an increased blood flow, is often a very annoying symptom. Bleeding from the nose is not infrequent; bleeding from stomach and rectum is rare. Patients usually have extreme numbness in their distal phalanges and a generalized burning sensation. Some may have Ménière's syndrome. A tendency to thrombosis, particularly to cerebral thrombosis, is quite marked because of the increased viscosity of the blood, probably due to an increase of calcium in the blood as recently reported by Roth, of the Mayo Clinic.

Diagnosis is established by the blood examination. On pricking an ear lobe or finger-tip the blood flows with difficulty and is thicker than normal. If it flows from a vein into a test-tube it coagulates much more rapidly than normally, and the amount of serum is extremely small. The number of red blood-

cells is usually about 7,000,000. Cases have been reported where it was as high as 12,000,000. Hemoglobin may be as high as 180 per cent. The blood-platelets are increased. There are no important characteristic changes in the white blood-cells. The disease may last many years, but in many instances the patient succumbs to intercurrent disease. Cases of polycythemia have been reported, which terminated as acute or chronic leukemia, again showing the interrelationship of affections of the hematopoietic apparatus.

DISTURBANCES OF THE LEUKOBLASTIC ELEMENTS

Diseases in which the leukoblastic elements are disturbed are known as leukemias. *Acute lymphatic* and *myeloid leukemias* are those most easily recognizable in the majority of cases. The acute lymphatic type sets in usually abruptly, or, at most, is preceded by only a few days of malaise. During malaise there may be epistaxis. A most noteworthy feature is that the patient often consults a dentist for an extraction because of severe toothache.

With the onset of symptoms there is marked tonsillitis, stomatitis, and pharyngitis. After a few days petechiæ may be found over different parts of the body, and there is considerable enlargement of the lymphatic glands and spleen. The temperature is high, and the patient may be stuporous, delirious, and have twitching of the various parts of the body, such as the arms and legs, resembling severe sepsis. Hemorrhagic diathesis may be marked, and bleeding from the mouth, and more rarely from other organs, is present. The enlargement of the glands and spleen point to the diagnosis of lymphatic leukemia, even without a blood examination, although the latter makes diagnosis more certain as small lymphocytes number 200,000 to 350,000 per cubic centimeter of blood. Blood-platelets are moderately diminished. When the symptoms are not so violent, there may be only a few petechiæ; the spleen and lymphatic glands, especially those of the groin, are only slightly enlarged, and the temperature is moderately elevated. In such cases diagnosis may be established only by blood examination.

The acute type is generally fulminating, terminating fatally within two or three weeks, sometimes within a week. The milder type may progress to simulate a chronic form. The acute type offers difficulty in differential diagnosis if it is encountered during the subleukemic or aleukemic state. We are confronted, then, with a classical clinical picture of lymphatic leukemia, but the blood shows leukopenia with small lymphocytes (70 to 80 per cent.) dominating. Such a picture establishes diagnosis. Although there may be hemorrhagic diathesis, the condition differs from thrombocytopenic purpura in that the number of blood-platelets is not considerabley reduced. In certain severe cases throat infection may be marked preceding other symptoms, and the disease may be treated for diphtheria or Plaut-Vincent angina. One must be ever on his guard not to diagnose Plaut-Vincent angina because of the presence of Plaut-Vincent organisms. They may be found in any smear obtained from a necrotic condition of the tonsils or pharynx.

Acute infectious mononucleosis (or *lymphadenosis*) is a possibility that must not be forgotten. It is known to occur in children as glandular fever, and has been frequently observed in adults. W. T. Longcope gave an excellent description of it, and, recently, L. D. Cady[5] described a number of sporadic cases, calling attention to the fact that many of them ran for a number of months with a persistent abnormal blood-picture. It is important for one to be familiar with the clinical and blood pictures of this disease because the symptoms may be severe and may simulate lymphatic leukemia. If a mistaken diagnosis is made, alarm is caused and possible later disgrace to the physician. The disease is acute in onset, with a temperature from 102° to 105° F., and malaise and pain over the lumbar region. One of our cases, a woman of fifty, had considerable pain over the sternum and long bones. There was a mild degree of tonsillitis, pharyngitis, and stomatitis. The appearance of the tonsils may simulate Vincent's angina, but the spirilli, although present, are never there in large numbers. On the second or third day of the disease the superficial, particularly the cervical and axillary glands, become enlarged. They may be characteristically larger

on one side than on the other, but seldom suppurate. The spleen is likewise enlarged. The disease lasts from seven to ten days, now and then two weeks. Exact blood studies in this condition were made by A. Downey and C. A. McKinley,[7] who made a tentative classification of the cells as follows: Type I, those not excessively enlarged, but varying in size and shape, highly differentiated from lymphocytes (Pappenheim); Type II, large cells, resembling plasma; and Type III, the largest cells, resembling leukemic cells.

The most characteristic feature is the moderate leukocytosis, or a normal count with 70 to 80 per cent. lymphocytes. In 1913 R. C. Cabot called attention to the so-called lymphocytosis of infection, a condition where a mild chronic infection persists with lymphocytosis, the percentage being reversed, with 60 to 70 per cent. lymphocytes that are usually of a normal character, and cannot be mistaken for leukemia. In certain cases the glands in the chest may be enlarged, giving rise to a hoarse cough and dyspnea, but when the size of the glands diminishes the alarming symptoms disappear.

Chronic Lymphatic Leukemia

Generally this condition offers no difficulty in diagnosis, either clinically or hematologically. Clinically, it is recognizable by a varying degree of splenic enlargement, never, however, reaching the size encountered in myeloid leukemia. The glands, particularly the axillary and cervical, possibly the inguinal and epitrochlear nodes, are enlarged. The tendency to hemorrhagic diathesis (although present) is not marked. The patient is pale, loses weight, and is easily exhausted. Skin manifestations of varying degree—a moderate brown discoloration and eczema-like eruptions similar to leukemic infiltrations of the skin—may be present, more frequently than in myeloid leukemia. Occasionally lymphatic infiltration of all organs is present. One often encounters an elevation of temperature with pneumonic signs in the lungs, but the condition proves to be only a lymphatic infiltration, although, of course, bronchial or lobar pneumonia may develop. It is most interesting that during the

period of acute symptoms the hematologic picture may change, producing a leukocytosis with polynucleosis. When the patient recovers from his pneumonia the picture of lymphatic leukemia returns. We had a case, a woman patient in this hospital, who suffered from chronic lymphatic leukemia. She had had recurrent attacks of pneumonia during each of which the leukemic blood-picture disappeared. Similar cases have been reported in the literature. *Any acute infection, including pneumonia, occurring in the course of lymphatic leukemia, may change the leukemic blood-picture to an ordinary polymorphonuclear leukocytosis.*

Chronic Myeloid Leukemia.—In this affection the spleen is immensely enlarged and may occupy almost the entire left side of the abdomen down to the pelvis. It is the largest spleen encountered, as a rule, in splenomegalic diseases. It may often be the cause of pain in the left abdomen and left chest, radiating to the shoulder. It may be the only symptom that causes the patient to consult a physician. The splenic enlargement, by causing pressure on the left diaphragm without resulting atelectasis of the left lung, may simulate pleural affection, an erroneous diagnosis which has often been made at the bedside. On palpation the spleen feels extremely hard and, due to its immensity, does not move on respiration. It may become acutely larger with perisplenitis; friction is heard over the splenic area, and there is generally an elevation of temperature, a condition that may occur during the course of the so-called blood crisis, during which time the number of leukocytes in the blood may reach 400,000, even more, and the enlarged spleen may fill the entire abdomen, simulating peritonitis. Such a condition may result if an overdose of radium or an overtreatment with *x*-ray is given.

Any chronic form of leukemia, especially the myeloid type, may have stages during which the number of leukocytes is only moderately increased; perhaps not at all. Only the abnormal white cells are increased, a finding that may go hand in hand with the general symptoms, or one that may be present only while the systemic symptoms are pronounced. During this period differential diagnosis is far from easy, and a careful

hematologic study, including that of oxidase reaction for myelocytes, is indispensable.

Other glands of the body in this condition are only slightly enlarged, although by a careful search one will find small glands in the supraclavicular region and slightly enlarged glands in the axillary region. Skin infiltration in myeloid leukemia is not uncommon. All forms of skin affection may be present, causing the patient to consult skin specialists, and the condition may go unrecognized unless the specialist examines the blood and finds the skin lesions to be of a leukemic nature. The leukemic infiltration of the skin and internal organs may be more outspoken than the splenic symptoms, and so mask the clinical picture. Through the courtesy of Dr. Joseph Tennebaum, we saw a case where he recognized the skin lesion as that of a myeloid leukemic nature, confirmed by the blood-picture. The infiltration later took place in the lungs and brain. Chronic myeloid leukemia may, if it lasts long enough, invade every organ of the body.

Instances of aleukemic myelosis with osteosclerosis of the entire skeletal system have been reported. An interesting case reported by Jores[13] concerns a thirty-four-year-old woman with a blood-picture of 1,430,000 red blood-cells, and 25 per cent. hemoglobin. There was marked sclerosis of the bones and an absence of bone-marrow. The spleen was immense and weighed 1600 grams. Histologically, the bone-marrow was replaced by fibrous tissue, and it was evident that both the aleukemic myelosis and the anemia were the result of fibrosis of the bone-marrow. It was impossible to decide which had been the primary and which the secondary cause.

The symptoms are mainly those due to the pressure of the enlarged spleen or to the involvement of other organs by the leukemic process and those due to the anemia. The blood-picture is the most conclusive diagnostic method, but we must know, as in all hematologic diseases, that the blood-picture may be normal at one or another of the examinations and, therefore, make diagnosis very difficult. We may quote a case of this character seen through the courtesy of Dr. Datnofsky, a man fifty years of age, who was well until three months ago, when

he suddenly developed a pain over the left side of the abdomen, with progressive weakness and loss of appetite. On examination a tumor mass, occupying the greater part of the left side of the abdomen, which could be definitely decided to be due to a splenomegaly, was found. Clinically, myeloid leukemia was suspected. To our surprise, however, his white-cell count was only 6000, and the most careful count revealed only 2 or 3 myelocytes. The rest was a normal blood-picture. We were inclined to change our diagnosis, believing we might be dealing with a case of Gaucher's disease, or, possibly, a tumor of the kidney. He was pyelographed by Dr. Leo Buerger, who found the kidney to be normal. The mass was considered to be a retroperitoneal sarcoma. Dr. M. Rosenthal examined the blood, and as there was nothing to point to leukemia, the diagnosis was still uncertain. A second blood examination by Dr. Rosenthal, and another in our office, showed the white-cell count to be 10,000 and 12,000, respectively. The differential count by Dr. Rosenthal showed 14 per cent. myelocytes and some myeloblasts, while we found 8 per cent. myelocytes, which cleared the diagnosis. This case well illustrates how difficult it is in the subleukemic state to make a diagnosis. Some advise puncturing the spleen or even the bone-marrow in these cases to establish diagnosis, but this is a procedure which, although done by some observers hitherto without danger to the patient, is one, nevertheless, we have not dared to practice.

The course of chronic myeloid leukemia is greatly influenced by *x*-ray treatment. Dr. I. S. Hirsch, who has had a great deal of experience with these cases, has seen cases in which both objective and subjective symptoms have disappeared after *x*-ray treatment for from four to five years. This observation is confirmed by many authors.

Acute myeloblastic leukemia is of great clinical importance, presenting difficulties to both clinician and trained hematologist. Frequently there is a prodromal period of weeks, during which the patient cries easily, experiences bleeding from the gums on the slightest trauma, toothache (necessitating an extraction), and pain over the sternum. He feels grippy and has a pain in

the throat, although the tonsils show no change. The condition progresses gradually, and the symptoms of hemorrhagic diathesis are more marked. Bleeding from the gums becomes severe and necessitates a constant holding of the handkerchief before the mouth, even during speech. Bleeding from the rectum, urethra, or uterus is not as common as in thrombocytopenia.

Coincidental to bleeding from the gums, the patient notices ecchymotic areas which he attributes to slight trauma. These are later so located that they are obviously not caused by trauma. The temperature rises, the patient is exhausted, and is forced to bed. Progress now is rapid, the temperature is higher, hemorrhage from the mouth is profuse, and bronchitis, tracheitis, and laryngitis may cause distressing choking symptoms. The patient may swallow blood into the stomach, with resulting hematemesis, simulating gastric hemorrhage with black stool. Numerous symptoms of mediastinitis and bronchopneumonia develop and the condition terminates fatally within a few days. Rarely hemorrhage to the brain occurs, the patient sinking into a stupor, and from stupor into coma.

The blood-picture is conclusive. The leukocytes number 40,000 to 50,000, seldom higher (as a rule, lower), myeloblasts predominating (50 to 80 per cent.). Blood-platelets are markedly diminished and there is a moderate degree of secondary anemia. With these clinical and hematologic findings differential diagnosis is not difficult, although some hematologists still deny the existence of myeloblastic leukemia and class it with lymphatic leukemias. Such a classification, however, is not acceptable because these cells show a positive oxidase reaction. It seems to us that in view of the fact that this cell is less ripe than the myelocytes, the term "myeloblast" is proper, and we should adhere to it.

At times myeloblastic leukemia is acute, running a fulminating course, with hemorrhages from the mucous membrane, rectum, uterus, mouth, nose, and conjunctivæ. The petechiæ are less outspoken, and the ulceration of the pharynx and mouth is not pronounced. The temperature is elevated. The leukocytes are not greatly diminished in number. Oligocythemia,

leukopenia, and a notable reduction of blood-platelets are present. Differential diagnosis lies between thrombocytopenic purpura and myeloblastic leukemia. It may be impossible to distinguish the conditions during life, and varying reports from the pathologists may be received after postmortem examination, so that a positive conclusion cannot be reached. Occasionally, these cases are submitted to splenectomy. The patient recovers, but within a few months the typical picture of myeloblastic leukemia develops and terminates fatally. Whipple, of the Presbyterian Hospital, New York, calls attention to one differential point, namely, that in thrombocytopenic purpura, although there is no leukocytosis, there is no actual leukopenia; whereas in myeloblastic leukemia there is a definite reduction in the number of leukocytes, to 2000 to 3000. Myeloblastic leukemia seldom runs a subacute course.

HEMATOLOGIC AFFECTIONS CAUSED BY SPLENOMEGALIC AND OTHER LYMPH-GLAND DISEASES

One of the most difficult diagnostic problems arises in cases where splenomegaly, with or without enlargement of the other glands, is present. Simple as it usually is to palpate a large spleen and superficial lymph-glands, it may be difficult to decide whether the enlargement of the spleen and hemolymph glands is a primary affection producing the hematologic disturbance, or whether it is secondary to another disease. In many instances it is difficult and most trying—in spite of all laboratory examinations—to state whether the enlargement is secondary to tuberculosis, syphilis, etc. Even biopsy may leave us in doubt.

SPLENOMEGALIES

The diagnosis of primary splenomegaly will always remain obscure because there is no known functional disturbance during life which can be universally attributed to a diseased spleen. Working with the spleen experimentally—by removing the organ or eliminating its function by some other means as in thrombosis—one finds that different animals, and animals of the same species, react differently. So, too, in the human being there

may be varying reactions. There may also be an enlargement of the spleen with identical pathology, owing to an entirely different systemic reaction. This is not surprising if one recalls that outside of the accepted work of Barcroft,[1] who showed the important rôle of the spleen in holding large quantities of blood, there is no other established function. Even this function, hemolysis, according to O. Lubarsch, is not verified.

There is reason to accept the view of Morowitz[22,23] that the spleen, like other organs of the body, has absolute and conditional functions; the organ may function under certain conditions, and not under others, analogous to conditional reflexes. Being part of a system (bone-marrow, hemolymph glands, and liver), its function may easily be taken over by another part of the system. This would explain why, as pointed out by Morowitz, nucleated red blood-cells, reticulocytes, and Howell-Jolly bodies appear in large numbers in certain instances, and not in others. The vascular system, particularly the endothelial cells of the small vessels, is demonstrated by the fact that bleeding ceases after splenectomy, as in thrombocytopenic purpura. This happens despite the fact that following the original rise there is a decrease in the number of blood-platelets. Cori attributes this to the influence of the spleen on the endothelial cells of the capillaries and their contraction.

Of the splenomegalic diseases which are of hematologic interest, we have mentioned myeloid leukemia, hemolytic icterus, and polycythemia. Here we shall describe, briefly, splenomegalic anemia. This affection is characterized by considerable enlargement of the spleen, a slight enlargement of the liver, and hardly any enlargement of the superficial glands.

These patients consult a physician for very vague symptoms; namely, weakness, tiredness, shortness of breath on slight exertion, and loss of weight. Objectively, they look anemic, the spleen is considerably enlarged, but is not painful as there is never a perisplenitis. As a rule there is no ascites and there are no icteroid manifestations. Urobilin and urobilogen in the urine are slightly increased. The icterus index is normal, and there is no increase of bilirubin in the blood-serum. There is

secondary anemia, the red blood-cells are smaller than normal, usually anisocytosis and poikilocytosis are present to a mild degree. The rouleaux formation is considerably lost. As far as the leukocytes are concerned, there may be a marked transitory leukocytosis, occasionally leukopenia. With the leukocytosis, there is frequently polymorphonucleosis. The diminution of blood-platelets is relative. The hemorrhagic diathesis is very slight. Neither the bleeding time nor the coagulation of the blood is disturbed. These are the pure splenomegalic anemias.

Banti's Syndrome With or Without Known Etiology

The form of splenomegalic anemia described by Banti is known as Banti's syndrome. He described it as characterized by three stages: (1) First, that of splenic enlargement, with a varying degree of anemia; (2) later an enlargement of the liver during which there are icteroid manifestations; (3) that of ascites, and cachexia with bleeding.

This clinical entity may be attributed to fibro-adenia of the spleen with a total disappearance of the pulp. The liver enlargement is entirely secondary. It has been found that a number of conditions give rise to a similar picture, secondary to other infections such as thrombophlebitis of the splenic vein, or of the portal vein, primary Laennec's cirrhosis of the liver, syphilis and tuberculosis of the spleen. In nearly all cases, with the exception of that described by Eppinger, the cause can be found for Banti's syndrome outside splenic fibro-adenia. Eppinger states that it is quite probable that in certain countries like Italy splenic fibro-adenia of the Banti type is frequent. In reality it is a rare disease, offering extreme difficulty in absolute diagnosis at the bedside. The final diagnosis, as in a case we observed in this hospital, depends frequently upon a pathologic study of the surgically removed spleen, or upon postmortem examination.

It is unjustifiable, clinically, to deny the existence of Banti's fibro-adenia as is done by some observers. One must, however, rule out the aforenamed affections, simulating Banti's fibro-adenia, before diagnosing this syndrome. It would be more nearly correct to name this affection Banti's symptom-complex with

known and unknown etiology, in view of the fact that there are a number of conditions with similar pathologic changes. For instance, if lues is the cause, it should be termed "luetic infection of the spleen with Banti's symptom-complex." If thrombosis of the spleen or portal vein is the cause, we should call the condition thrombosis of the affected vessels with Banti's symptom-complex. *If no etiologic factor is known, it should be called primary Banti's syndrome.* Such a classification would have a definite prognostic and therapeutic significance.

There is certainly no reason to identify Laennec's cirrhosis with Banti's disease. In the latter, the spleen is the primary seat of the affection, while in the former, the liver is primary and the spleen secondary. There is no case on record to make one think even clinically of Banti's disease, without enlargement of the spleen. There are many cases where a diagnosis of Laennec's cirrhosis is justifiable although the spleen may not be enlarged. Furthermore, anemia is a late manifestation, and if present at all, is due either to advanced dysfunction of the liver, or to associated bleeding either from hemorrhoids or ruptured esophageal varices. In primary Banti's disease, anemia develops as part of the disease without any bleeding. When bleeding does occur, it may come from the stomach, intestines, or nose, and may be so profuse and repeated as to simulate bleeding from gastric ulcer or gastric carcinoma. Bleeding from the stomach in the course of Banti's disease may be mistaken for bleeding gastric ulcer or carcinoma. Many years ago, we observed a case repeatedly treated for gastric ulcer because of bleeding. The marked splenic enlargement led us—without being able to determine a causative factor for the size of the spleen—to diagnose it Banti's disease. Dr. Joseph A. Blake, Roosevelt Hospital, removed the spleen and the patient recovered. Three years later, the hemorrhages repeated themselves and the disease eventually terminated fatally. We recall another case, a boy whose spleen was removed because of rupture due to trauma. He recovered, but when nineteen years of age developed fatal bleeding. At postmortem, esophageal varices were encountered.

Certain Italian observers have found that in some individuals, the removal of the spleen may induce fatal bleeding later in life. The cause of such bleeding cannot be ascertained. We are of the opinion that in the cases observed by us the esophageal varices probably existed before, or continued to exist after the removal of the spleen, and happened to rupture. We think it scarcely probable that there is a direct relationship between splenectomy and bleeding later in life. If there were, doubtless many more cases would have been reported, as splenectomy has been practised for more than fifteen years.

During the second stage, there are icteroid manifestations, or the skin may be dirty yellow or sallow. The urine invariably contains a large quantity of albumin and granular hyaline casts. Urobilin and urobilogen are not found in Banti's disease as a rule, and if found the quantity is small. Where cholangitis of the liver complicates the disease, the urobilin and urobilogen are increased in all stages. The blood changes are not characteristic. During the first stage they are those of chloranemia: low hemoglobin 40 to 50 per cent., and the red blood count may be almost normal. After a short while, the patient looks pale, there is a moderate anisocytosis and poikilocytosis. Leukocytosis is the rule, monocytes usually predominate and normoblasts are never found.

Gaucher's Splenomegaly

This type of splenomegalic disease was described first in 1882 in various countries. Brill, Mandelbaum, and Libman studied it carefully, and showed that the characteristic large cells of the spleen may be found also in the bone-marrow and lymph-nodes. The etiology is unknown. Its onset is insidious before the thirteenth year and the course is chronic. It is encountered frequently in several members of a family.

There are no symptoms early in the disease, but later there is progressive weakness with hemorrhagic diathesis, particularly of the mucous membrane and skin. Pappenheim mentions a case of a fatal esophageal hemorrhage occurring two years after splenectomy. The most important symptom is splenomegaly. The patient will often walk around and complain of only slight

pain in the left hypochondrium. On examination, an immensely enlarged spleen is found. The spleen is occasionally larger than that in myeloid leukemia, and yet, until told of his enlarged spleen, the patient may not be aware that he is sick. When he attracts the interest of many physicians, he begins to brood, worry, and develop other symptoms.

The liver is moderately enlarged, but there is no enlargement of the lymph-nodes. E. P. Bernstein was the first to diagnose a case by puncturing the spleen and so discovering the characteristic large cells, a procedure that should not be encouraged because of the danger of severe infection and hemorrhage. Jaundice is not present, as a rule, although it may be encountered and may be very marked. Large endothelial cells are also found in the bone-marrow and may so crowd it as to cause severe pain in the bones, and lead to spontaneous pathologic fracture.

In the summer of 1927 a man of forty-eight was admitted to this hospital with a diagnosis of gall-stones. He was markedly icteric, had an enlarged liver, and considerable enlargement of the spleen. The spleen, however, was not of the size usually found in Gaucher's. We considered the affection hemolytic icterus complicated by biliary colic, with or without calculi. During the patient's stay in the hospital he developed progressive anemia, had a moderate elevation of temperature, and persistent pain in the right hypochondrium. The degree of icterus varied from day to day. The stool was moderately icteric at times. The urine contained urobilogen and urobilin, as well as bilirubin from time to time. The blood-serum showed both direct and indirect Hijmans Van den Bergh reaction and an increased icterus index. Some examinations revealed no change in the red blood-cells; others, a diminution of resistance. This was peculiar, indeed, as we expected diminished resistance on every examination. Eppinger likewise reports cases of hemolytic icterus where the resistance of the red blood-cells was unaltered.

Hematologically, there was evidence of secondary anemia, but there was no hemorrhagic diathesis. We could not succeed in encouraging the patient to have a splenectomy, and he left

the hospital. A few weeks later he went to Mt. Sinai Hospital and the spleen was removed. Remarkably enough, Klemperer reported it to be of a Gaucher type. This was a case where, first of all, icterus was the leading symptom. Biliary colic, moderate enlargement of the spleen, urobilin, and urobilogen were present in the urine—phenomena characteristic of hemolytic icterus. Yet, pathologically, the spleen was of a Gaucher type.

In the majority of cases there is a peculiar, almost characteristic, pigmentation over different areas of the skin. W. H. Schultz reported a case who died of diabetes with a high degree of lipemia. The spleen showed an entire disappearance of the pulp and a small number of follicles. The cells resembled the endothelial cells of the Gaucher type. This is quite interesting because of the splendid studies of L. Pick, aiding so much in an understanding of this disease. Pick found the most important pathologic characteristic to be a lipoid substance in the cells. Since Schultz's publication, Lutz has reported a similar case.

Hodgkin's Disease

Of the other hematologic changes of the lymph-glands, Hodgkin's disease interests us most. It is called lymphogranuloma or lymphoblastoma by Minot and Isaacs. Up to the time that Paltauf and Sternberg described its exact clinical and pathologic picture, the differentiation between this form of adenopathy, lymphosarcoma, luetic, and tuberculous adenopathy was very indefinite.

Credit must be given first to Virchow who differentiated lymphogranuloma from sarcoma of the lymphatic glands with so little microscopic aid. There are authors who dispute the distinction, but this is unjustifiable from both clinical and therapeutic standpoints.

The disease occurs more often in men than women, and usually between the ages of twenty and fifty, running a chronic course. Before the era of *x*-ray and radium treatment the average duration of life was estimated from three to five years, but there is no doubt that now, due to treatment, life can be

prolonged considerably. We know a case lasting twelve years, with slight recurrences. The patient is still very comfortable.

The onset and clinical symptoms vary greatly. The most typical cases begin more or less abruptly. The patient, or his friends, notices that the glands of both sides of the neck or submaxillary glands are enlarging, and that the patient is pale. He may or may not have slight subjective symptoms, such as weakness or tiring readily. The glandular enlargement may be the only sign for a long time. On palpation the glands are usually felt as a semisolid conglomeration of small glands over which the skin is freely movable. They are not painful and are easily differentiated from tuberculous glands, which coalesce, suppurate readily, and over which the skin is generally red and adherent.

If a careful *x*-ray examination of the chest is made, one will encounter a noticeable increase in the hilum shadow with marked demonstration of the shadow, and, sometimes, as pointed out by Wessler, a rounded or elongated, illy-defined shadow in the region of the second and third interspace, particularly to the left. Wessler considers this characteristic of Hodgkin's disease. This is of the utmost importance in treatment because it is quite likely that the enlargement of the glands in the neck is an expression of a primary invasion of the glands in the chest. It is of moment for another reason. In Hodgkin's disease the lymphatic involvement in the chest generally progresses slowly, unlike that of lymphosarcoma, which is very rapid. Lymphosarcomatous glandular enlargement in the chest gives rise to severe chest pressure symptoms and to displacement of the neighboring organs. In glandular enlargement in the chest, due to Hodgkin's disease, although a size quite equal to that of lymphosarcoma may be reached, the pressure symptoms are not as marked because the rapidly growing lymphosarcoma compresses the different organs—blood-vessels, trachea, lungs, etc.—abruptly, giving rise to symptoms of compression and enlargement of the superficial veins of the thorax, hoarseness, etc. The glands in Hodgkin's disease grow slowly and the organs have a chance to accommodate themselves and hence do not give rise

to such pressure symptoms. Roentgenologically and fluoroscopically we find that lymphosarcomatous compression of the trachea causes considerable atelectasis, whereas this need not be encountered in Hodgkin's disease. In the more favorable cases the enlargement is confined to the superficial glands in rotation: to the neck, axilla, groins, and, rarely, to the epitrochlear glands. When there is general glandular involvement, with the largest glands those in the neck and axilla, we may be fairly certain, clinically, that we are dealing with Hodgkin's disease.

Hodgkin's disease can be differentiated, clinically, from lues, because syphilis, during a stage of glandular enlargement, gives rise to skin and mucous membrane manifestations. When there is only a glandular enlargement the glands usually enlarged are those in the groins.

They can be differentiated from tuberculous glands, first, by the fact that they are not painful and the skin is not adherent over them, and, second, the glands of the groin and those of the axilla, if increased, are never as large as in Hodgkin's disease.

Long before glandular enlargement the patient may complain of itching of the skin, particularly over the lower extremities, causing actual scratch wounds. Occasionally there is a brownish discoloration over different skin areas. The facies are sometimes characteristic, mostly of a feminine type, and not hairy. There is a tendency to the status thymicolymphaticus. Adenoids are present and the tonsils are frequently enlarged. In some instances the superficial glands are small and the visceral glands are most affected. These cases offer great difficulty in differential diagnosis.

Occasionally only the glands in the chest are enlarged, causing pressure symptoms, as noted, with a hoarse, brassy cough, and excessive expectoration, loss of weight, and clubbed fingers, simulating, clinically, bronchiectatic abscess of the lung, sometimes most difficult to differentiate roentgenologically. Pressure on the vessels in the thorax causes only lateral or bilateral effusion in the pleuræ.

Less frequently the glands in the abdominal cavity become enlarged, giving rise, possibly, to large palpable masses, associated with enlargement of the spleen, liver, and marked anemia. The enlargement of the abdominal glands may cause pressure on the biliary ducts, producing marked icterus, or they may press the portal vein and give rise to ascites. They may also cause pressure on the vena cava with edema of the trunk and lower extremities, or pressure on the thoracic ducts, giving rise to chylous ascites. Where the superficial glands are not enlarged, with no possibility of biopsy, the diagnosis may remain obscure until postmortem examination. Biopsy by only the most skilful pathologist should be relied upon. Although the presence of red cells, eosinophilic cells in the glands, and giant cells would seem to be so characteristic, a section is not infrequently seen by several competent pathologists, one of whom reports Hodgkin's disease, and others some inflammatory condition. The diagnosis may be still more difficult if, as pointed out by Sternberg many years ago, and recently by S. Ginsburg[9] of Montefiore Hospital, the glands invade the spinal cord, leading to the erroneous diagnosis of tumor of the spinal cord. As expressed by Ginsburg, Hodgkin's lymphogranuloma is a systemic disease and may affect any part of the body where there are lymphatic glands.

Another symptom complicating diagnosis is the tendency to elevation of temperature. A moderate elevation may be present throughout, awakening a suspicion of tuberculosis. In the majority of cases, however, the temperature curve is that of a moderately septic nature. It may be 103° or 104° F. in the afternoon and come down the next morning to normal. Pel-Ebstein first described this type and it is known as the Pel-Ebstein temperature curve.

The blood-picture varies a great deal. Throughout the entire course of Hodgkin's disease there is usually evidence of secondary anemia with moderate leukocytosis. There may be a transient, very high leukocyte count, sometimes 50,000 to 60,000 per cubic millimeter, complicating diagnosis.

THROMBOCYTOPENIA

This is a most interesting affection because, since the studies of Kaznelson, who advocated the removal of the spleen for this disease, the studies of Franke have done much to clarify it. In 1740 Werlhoff described the clinical symptoms fully and named the affection morbus maculosus hemorrhagica. His original clinical description holds good today, and the affection later became known as Werlhoff's disease.

Not until the exact part blood-platelets play in hematology in general, and in Werlhoff's disease in particular, was it possible to understand thrombocytopenia. Thrombocytes were considered imperfect or deformed red cells, or the débris of red cells, for a long time. In 1877 Hayem, in France, named them hematoblasts because he believed them to be youthful forms of red blood-cells. In 1881 Brohm observed 2 cases of Werlhoff's disease and was the first to point out that in it the so-called hematoblasts were markedly diminished. Krauss, a pupil of Brohm, made a careful study of the relationship of hematoblasts to Werlhoff's disease, and to him belongs the credit of pointing out that the reduction in number of this blood element is a characteristic feature of it. Had Krauss been familiar with the work of Bizzozero, who, a year before, described hematoblasts under the name blood-platelets, designating them the third independently formed element of the blood, and stating that an aggregation of blood-platelets is the underlying foundation of every thrombus, he would have correlated the diminution of blood-platelets more closely with this disease. This was left to Denys, a Belgian pathologist, who showed that the diminution of blood-platelets is the cause of bleeding. The greatest credit in this country belongs to W. W. Duke. He pointed out emphatically and conclusively, after extensive experimental and clinical studies, that diminution of blood-platelets is the cause of hemorrhage in Werlhoff's purpura.

Duke, Minot, Franke, and others have shown conclusively that if thrombocytes in the blood are reduced below 50,000, even a slight trauma causes ecchymosis. If the blood-stream is slowed, they adhere to the blood-vessels and cause thrombosis

during life (Ascher). Wherever there is a foreign body in the tissues, thrombocytes collect around it and are the first factor in coagulation. The agglutination power of the thrombocytes explains the retractile property of the blood-clot.

Thrombocytopenia may occur in different forms clinically. It may be a mild purpura hemorrhagica, with a periodic moderate bleeding from the gums or nose, and ecchymotic areas as well as purpuric spots over various parts of the skin. The coagulation time is considerably delayed, the retractility of the blood-clot is diminished, the Rumpel-Leede-Hess tourniquet test is positive, and the blood-platelets are reduced in number. They may be 50,000 or less. There may be a moderate elevation of temperature and a general systemic sensation of tired feeling. Although the number of blood-platelets may not increase to a large degree, the symptoms last several weeks and then disappear. These cases, after a few attacks, may clear up completely, although throughout life they show some hemorrhagic diathesis. The affection may occur during any period of life and is somewhat more common in the female than in the male, and occurs more often at the beginning of puberty and the approach of menopause. This mild form of purpura is emphasized particularly because the present tendency is to associate thrombocytopenia with splenectomy, and subject even mild cases to this not indifferent operation. We are strongly against such cases being splenectomized.

It is clinically important that purpura-like or thrombopenic-like affections exist where the reduction of blood-platelets is not marked or, if so, only in proportion to the reduction of hemoglobin and red blood-cells. Henoch's purpura is such an affection. In addition to the, at times, very scant purpuric manifestations of the skin there are abdominal cramps and moderately bloody stools without tenesmus. Often it is diagnosed with great difficulty because the abdominal cramps may precede the purpuric-like eruptions by several days. The pains have a strong tendency to localize in the ileocecal region, simulating appendicitis, and sometimes cause an unnecessary operation. Although simulating appendicitis, there is never rigidity over the rectus

muscle, and the vomiting in the cases we have encountered has been rather a protracted symptom, unlike that of appendicitis, where in the majority of cases it ushers in the disease. In a case we observed suffering repeated attacks, bloody stool was present upon the termination of each attack. There was evidence of diathesis (called arthritism by the English). The mother of this patient was subject to severe attacks of giant urticaria, one attack involving the larynx when she was reddened with suffocation and relieved by adrenalin subcutaneously. The paternal grandmother and the father had asthmatic attacks.

One must also add the so-called Schönlein purpura to this group. It manifests itself by joint involvement, an elevation of temperature, and a purpuric rash over the body. Because of the joint involvement, it has been called rheumatic poliosis, but "rheumatica" is unjustifiable. R. Ottenberg points out rightly that the affection has nothing in common with polyarticular rheumatism. It does not respond favorably to salicylates, does not affect the valves of the heart, the pericardium, or pleuræ, and the joints are never as painful as in polyarticular rheumatism. There are cases on record of endocarditis associated with this disease, but one is more inclined to believe the patient was afflicted with both diseases and that the Schönlein purpura had nothing to do with the endocarditis.

The form of thrombocytopenia in which one is most interested is that where splenectomy is of great therapeutic value. The onset is abrupt and the affection is quite common in girls at the age of puberty. The first manifestation may be prolonged bleeding from the uterus. Unlike the so-called innocent protracted menorrhagia, it leads to considerable anemia. We know how much blood a woman can lose during confinement, and during her menstrual periods, without evidence of anemia, indicating that a protracted physiologic loss of blood is compensated quickly by the blood-making organs, *whereas in thrombocytopenia, menorrhagia has no such compensatory mechanism, and hence there is an anemia.* Menorrhagia, anemia, ecchymosis, and petechiæ may precede bleeding from other areas. It is extremely important to recognize these cases because at this stage, if other

phenomena like the reduction of blood-platelets, the diminished retractility of the blood-clot, and the Rumpel-Leede-Hess tourniquet signs are present, splenectomy may prevent further symptoms, and is at this time least dangerous.

We saw a girl of fifteen, in whom bleeding from the uterus and anemia preceded the skin manifestations and bleeding from the gums and mouth, by many weeks. Later there were petechiæ all over the body, bleeding from the gums, and a marked, rapidly advancing secondary anemia. The girl was an only child and the parents would not permit splenectomy during the early stage. Done, in the active stage, although preceded and followed by transfusion it terminated fatally within twenty-four hours. In man, hematuria may precede the outbreak of other symptoms.

In the so-called fulminating purpura, hemorrhages from practically all surfaces—mouth, rectum, vagina, etc.—petechiæ, and ecchymosis are present from the start, with an elevation of temperature, a reduction of the blood-platelets, possibly to less than 10,000, and a marked reduction in the number of red blood-cells and often of the white blood-cells. True aleukia does not exist, thus differentiating the fulminating or malignant purpura from aplastic anemia and subleukemic anemia.

Rosenthal studied the blood-picture in various types of blood disease, accompanied by purpura, and divides purpura into three main groups:

1. Purpura characterized by a diminution of blood-platelets with or without alteration of function.

2. Purpura due to some change in the function of the blood-platelets without a diminution of number.

3. Purpura due to changes in the capillaries.

The blood-picture of the first is diagnostic in cases of acute and chronic thrombocytopenic purpura, acute and chronic aplastic anemias, and symptomatic thrombocytopenic purpura. The second group (chronic hereditary thromboesthenic purpura) is rare. The third main group is purpura due to conditions affecting the capillaries.

The classification is useful, explaining conditions in which

bleeding and skin manifestations occur without a diminution of the blood-platelets. It also explains conditions where bleeding ceases, although the blood-platelets are still reduced in number. It indicates that in one case the condition of the capillaries is affected despite the normal number of blood-platelets, or the blood-platelets are in an asthenic state, or below par. The other cases with cessation of bleeding and a great loss in the number of blood-platelets, would indicate that the quality of the capillaries and the blood-platelets is normal, or better than normal—hence no bleeding.

Malignant thrombocytopenia must be differentiated from myeloblastic subleukemic leukemia, sepsis, and agranulocytic angina, as well as from aplastic anemia. Leukocytes predominate. Frequently there are from 10 to 15 per cent. eosinophiles.

The pathogenesis of thrombopenia is unsettled. Kaznelson believes that the thrombolytic action of the spleen is the primary factor and bases his assertion on the fact that the removal of the spleen is a curative agent and because, in these cases, a marked increase in destroyed blood-platelets is found in the sinuses of the removed spleen. He states as proof of his contention that in all cases the spleen is enlarged. This, however, does not correspond to our clinical experience. There are, undoubtedly, cases with splenic enlargement, and many cases in which the spleen is not enlarged at all. Even after removal it does not show any evidence of enlargement or disease. That the primary affection does not lie in the spleen seems proved to us, further, by the fact that the spleen is seldom enlarged in the malignant or so-called fulminating thrombocytopenia, although often enlarged in the benign type and in symptomatic purpura. It is true that splenectomy causes a disappearance of the subjective symptoms; but it is equally true that the increased number of blood-platelets after splenectomy (which reach 150,000, 200,000, perhaps 400,000) endures only for a short period of time. After a lapse of several weeks they drop to 50,000 or 30,000, and bleeding does not recur. The loss of retraction of the blood-clot is permanent despite splenectomy, and one would conclude, therefore, that the primary detrimental effect

of the spleen on the blood-platelets is not the cause of the symptoms, but the quality of the blood-platelets. *The megakaryocytes, for some reason, produce blood-platelets of an inferior quality that are easily destroyed by the spleen before they reach the circulating blood.* Hence the small number of blood-platelets. Following the removal of the spleen (the destructive agent) all the blood-platelets reach the circulating blood and after several weeks the reticulo-endothelial cells assume the function of the spleen in destroying blood-platelets, so that a lesser number reaches the circulation. However, the reticulo-endothelial cells in the other hemolymph glands are not wholly effective in destroying blood-platelets. Those that exist have a chance to mature, and the physiologic property of the remaining thrombocytes is maintained. Although small in number, these thrombocytes have a compensatory function which causes a disappearance of the symptoms. In other words, *splenectomy qualifies one-fifth or one-sixth of the normal number of thrombocytes to carry out their function.*

Franke thinks there are two forms of purpura, one where the thrombocytopenia is due to a failure of the megakaryocytes to produce enough blood-platelets, and the other where the affection lies in the capillaries proper. In the first, there is a total reduction of thrombocytes; in the second, the reduction goes hand in hand with oozing from the capillaries. This oozing and secondary anemia are main factors, and the thrombocytes are only relatively diminished. In the former, too, the blood-platelets have pathologic characteristics, most of them being larger than normal, whereas, if the condition is due to capillary oozing, although the number of blood-platelets may be reduced, the appearance is normal.

Mironescu and Perlstein observed a case of fulminating purpura in a thirty-eight-year-old woman. In addition to hemorrhages and blister formation over both forearms, there was a marked reduction in the blood-platelets and an increase in neutrophilic leukocytes. Autopsy revealed degeneration of the lymph-cells in the spinal ganglia of the lower cervical and dorsal regions. There was distinct chromatolysis and interstitial infiltration, as well as hyperemia and thickening of the vessel

walls. Because of the well-known relationship of the spinal ganglia to the innervation of blood-vessels, these authors assume that in their case a general infection resulted in an injury to the blood-vessels and the spinal ganglia, thus leading to the clinical picture of purpura.

Where thrombocytopenia is due primarily to an affection of the capillaries, splenectomy has no beneficial effect.

TREATMENT

Secondary Anemias

The treatment of secondary anemias depends upon the underlying cause of the anemia. First, of course, comes anemia due to hemorrhage. Absolute quiet should be enforced in the restless patient by the administration of morphin. The next step, if the patient continues to bleed, is blood transfusion. This not only serves as a hemostatic, but replaces fluid and stimulates erythropoiesis, thus causing the blood formation to return to normal. Some authors advise direct blood transfusion. This may have a beneficial effect, but the Lewisohn citrated blood method is easier and has shown its efficacy very well.

When the oozing continues, and recovery is slow in gastro-intestinal hemorrhage, surgical intervention has to be resorted to. When recovery begins, there is a more rapid increase in the cellular element than in the hemoblogin, due to the fact that the blood absorbs fluids from other tissues and so dilutes the hemoglobin. As a rule, some four to six weeks are required for the blood to regenerate after hemorrhage. In women it takes place more rapidly than in men. Children tolerate bleeding badly, and transfusion should never be delayed.

It is understood that in the course of hemorrhage fluids must be replaced. If the patient bleeds from the lungs or lower bowel, plenty of fluid may be allowed by mouth. If the bleeding is gastric or eosophageal, fluid must be replaced by hypodermoclysis, Ringer solution 350 to 500 c.c. Enteroclysis of normal saline solution by the Murphy drip method is generally beneficial, but if the bleeding comes from the stomach or intestines,

it may not be well tolerated and, therefore, have to be discontinued. When the bleeding is from the stomach or colon, thorough lavage of these organs may have to be resorted to. Whether lavage should be practised in gastric hemorrhage has long been a moot question because of the fear that the introduction of the tube may increase the hemorrhage. This has some justification where there is reason to believe that the cause of bleeding is a deeply penetrating gastric ulcer. The introduction of the stomach-tube might cause a perforation, but these cases are accompanied by severe pain in addition to the bleeding, and lavage is contraindicated. Generally, the bleeding comes from a ruptured vessel without perforation, and the accumulated clots in the stomach do not allow that organ to contract. Therefore, the bleeding is increased. A thorough lavage causes the stomach to contract and may stop severe bleeding where every other method fails. Lavage, according to some authors, is best done with hot water; others advise ice water. We believe ice water has the better effect on the contractility of the stomach. Some observers advise adding adrenalin or tincture of iron chlorid to the water, but we do not believe either of these has any special effect. In fact, we think if insufficient adrenalin is given it has no effect; if too much, it may be absorbed and raise the blood-pressure, increasing the bleeding. The secondary dilatation effect of adrenalin, also, may increase it.

Other secondary anemias are treated according to the underlying cause. Drugs which encourage the regeneration of the blood, particularly when the hemoglobin is low, are the iron preparations. These have long been known to have a specific effect in chlorosis. An advance in iron treatment of moderate and severe secondary anemias, particularly in children, as well as in the treatment of convalescent patients requiring a tonic and roborant, deserving detailed description is that brought about through the work of Baudisch and Welo[2] of the Rockefeller Institute. They prepared magnetic iron oxid from magnetite ($FeO\ Fe_2O_3$) oxidized to 300° C. in a stream of oxygen, obtaining a water-free reddish-brown powder with a strong magnetic power. This powder has the formula of Fe_2O_3. Upon further

heating to 500° C., the strongly positive magnetic iron oxid changes into an unmagnetic iron oxid of the same chemical formula, Fe_2O_3. Roentgen photography has shown that the molecule of the magnetic powder is cubic in structure, helps the growth of certain bacteria, and is, therefore, strictly active. The unmagnetic powder is rhomboid in shape, does not influence the growth of bacteria, and is negative.

Bickel, van Ewyek, and Tennebaum,[3, 4] have prepared a form of active iron similar to that of Baudisch and Welo which is known commercially as "Siderac." Bickel with his co-workers, have shown that its effect upon the C–N ratio in the urine is to increase it by the diminution of nitrogen. Moldawski,[21] of the Czerny Clinic, Berlin, was the first to show its blood regenerative effect, and that it might excel other methods of therapy for anemia in children. Its effect is similar to that of arsenic, but it is of greater advantage in that it is non-toxic when given by mouth. It may be used not only for its effect upon hemoglobin and red blood-cells by influencing general metabolism in the body, but as a roborant and tonic. The junior author[10, 11, 12] was the first to show its effect upon the general metabolism of patients, finding the following results in adults similar to those first reported by Bickel and his co-workers experimentally:

(*a*) Improvement of food absorption in the gastro-intestinal tract.

(*b*) Limitation of protein oxidation.

(*c*) Retention of protein.

(*d*) Increase of C–N ratio.

(*e*) Like other inorganic iron correcting compounds, it definitely influences growth.

Animal experimentation and clinical observation have shown that the tonic effect on metabolism of this iron preparation is connected with an optimal dose. It is advisable for the practitioner to start, as the junior author did, with small doses, 5 mg. per day per kilogram of body weight, gradually increasing the amount to three times a day, 5 mg. per kilogram of body weight.

Pernicious Anemia

The disease at present attracting most attention is pernicious anemia. The treatment of this affection, due to the epoch-making laboratory work of Whipple, Rubscheit-Robbins, and Hooper, and the clinical work of Murphy, Minot, Cohn, and their associates, has now been placed on a firm basis, and the results are most encouraging. Although there is sufficient literature on the treatment, its importance is such that the treatment as recommended by Minot and Murphy is set forth. The basis of their suggested daily dietary its represented by:

120–200 gm. of calves', beef, or chicken liver
400 gm. of fresh fruit
125 gm. of red muscle meat (beef heart desirable)
Not less than 300 gm. of fresh vegetables (particularly spinach, asparagus, cabbage, lettuce, and tomatoes)
Not more than 70 gm. of fat (avoiding cheese, bacon, fried food, cream, and butter)
Sparing use of sugar
Starchy foods to taste, avoiding grossly sweet foods
Not more than 240 gm. of milk, and avoid excess of salt
A complete day's rations would be:*

Breakfast

	Approximate weight in grams
Liver or kidneys, broiled	100
Oatmeal, 2 heaping tablespoons cooked, or dry meal	18
Milk, 3 tablespoons	45
Sugar, 2 level teaspoons	10
Toast, 3 slices (each slice 4 x 2 x ¼ inches)	30
Butter, 1 level teaspoon or a piece 1 x 1 x ½ inches	5
Fruits, choice of	
(*a*) Orange, average size	120
(*b*) Strawberries, 5½ tablespoons	180
(*c*) Grapefruit, one-half of one very large one	200
(*d*) Peach, 1 large one	120

Dinner

Beef, steak or roast, trimmed of fat, a very large serving	120
Vegetables, freshly cooked, as spinach, string beans, cabbage, tomato, etc., 2 average portions or 5 to 8 tablespoons	250
Potato, baked, medium size	130

* Taken from Pernicious Anemia, Beaumont S. Cornell, Duke Univ. Press, 1928.

Bread, 2 slices (each slice 3 x 4 x ½ inches)	70
Salad, pineapple, 2½ slices of size in cans	140
Lettuce, big helping	75
Pudding made of	
(1) Gelatin, 1 teaspoon, dry weight	2
(2) Rice, boiled, 2 heaping tablespoons	160
(3) Raisins, 20 large ones	50
(4) Milk, 2 tablespoons	30
(Fruits may be put into such a dessert and raisins eaten separately)	

Supper

Liver soup, composed of	
(1) Liver, minced	100
(2) Milk, 1 tumblerful	220
(3) Flour (white) 1 teaspoon	4
(4) Butter, 1 rounded teaspoon or a piece (1 x 1 x ⅞ inches)	10
Lamb, roast, without fatty parts, 2 small slices	60
Macaroni, boiled, 3 tablespoons	150
or	
Potato, a small one, or rice, 1 heaping tablespoon	80
Vegetables, fresh, 2 average portions, 5 to 8 tablespoons	250
Uneeda biscuit or triscuit, 4	25
Butter, 1 level teaspoon or a piece 1 x 1 x ½ inches	5
Choice of	
(*a*) Strawberries, 7 tablespoons	225
(*b*) Orange, a large one	150
(*c*) Apricots, or prunes, stewed, 2 tablespoons	100
Sugar, 2 heaping teaspoons	20

This dietetic treatment must be carried out with the strictest attention to detail if the desired results are to be obtained. The favorable effect is noticed within ten to fourteen days usually. Subjectively, the patient feels he is regaining strength and can attend to his work. The formerly depressed pernicious anemia patient, with his despondent look, now greets one with a smile and an expression of hopefulness. In other words, there is an absolute remission of the disease. The blood-picture shows, first, an increase in red blood-cells as compared to the hemoglobin, so that the color index comes back to 1.0. The shape of the red cells begins to return to normal. The urobilin in the urine diminishes, as does the bilirubin in the blood, indicating that hemolysis has ceased, and as improvement continues the number of red blood-cells and the hemoglobin increase. There are cases

on record where the hemoglobin has come up to 110 per cent. and the red blood-cells above 5,000,000. A few cases have been recorded where polyglobuli resulted during the course of treatment.

A very interesting feature of improvement is the increase in eosinophiles. They go up to 15 per cent., perhaps 20 per cent. One of our cases shows 18 per cent., the increase being maintained—the lowest count being 11 per cent.

Minot, Murphy, Cohn,[20] and their associates lay great stress upon the increase of reticulocytes in the blood in cases successfully treated. They conclude therefrom that the Whipple conception of pernicious anemia due primarily to the weakened stroma of the red blood-cells and that liver diet strengthen the red cell and allows it to become mature, is correct. It is remarkable that in a case we studied exhaustively we could never demonstrate an increase of reticulocytes. In our case early improvement, both subjectively and objectively, was marked. If the extract was added to the boiled liver, the patient showed signs of erythema nodosum over various areas of the body, but the lesions, as in polyarticular rheumatism, were confined to the lower extremities and around the joints, and were painful. There were also symptoms over the right kidney suggesting renal colic. The urine contained large quantities of uric-acid crystals, and the blood showed uric acid 4.6. We discontinued the liver extract, and gave liver proper in half quantity, whereupon the symptoms disappeared. The uric acid in the blood came down to 2.4, and the blood-picture likewise changed. The hemoglobin, which had been about 70, came down to 55, and the red blood-cells were greatly reduced in number. Eosinophiles were never lower than 11 per cent. During the time these symptoms were present—and we consider them to have been due to the increased uric acid—there was a field under the microscope in which the white cells showed remarkable deterioration. The nuclei were separated from the rest of the cell so that in certain areas segmented parts were seen, and the rest of the cell in other areas, a phenomenon difficult to explain.

It seems plausible that the breaking down of the white cells

was responsible for the increased uric acid in the blood, and the uric acid symptoms. An increase of normal leukocytes does not cause an increase of uric acid in the blood. The excess uric acid is held by the white cell and is not given up. When the leukocytes are of pathologic character, as in leukemia, they part with the uric acid and allow it to circulate freely in the blood or tissues. *We believe that the broken-down white cells seen in the field, in our case, were responsible for the increase of uric acid in the circulating blood and the existing symptoms.* We have not yet encountered this phenomenon in the literature, and it may have been due only to an idiosyncracy on the part of the patient. It is worth mentioning because if, in the course of treatment, symptoms of an increase of uric acid manifest themselves, it becomes necessary to reduce the liver intake. It seems, too, that patients who have an idiosyncracy do not improve as well as those who have not. Our case proves this. He is better, subjectively, but because he cannot get large enough doses of liver his hemoglobin stays at 55 per cent., his red cells at 3,000,000, and the eosinophiles at 11 per cent. The reticulocytes are not increased. The appearance of the red blood-cells, contrasted to what it was originally, is very much better. There are no megakaryocytes or macrocytes. There are only very moderate poikilocytosis and anisocytosis. In cases of this kind iron also should be administered, and we believe such cases should be encouraged by repeated blood transfusions. In addition to the liver treatment dilute hydrochloric acid, in doses of 15 drops in water, to be sipped with each meal, should be given. This often relieves epigastric distress.

The results of the liver treatment of pernicious anemia thus far are chiefly those of improvement of the blood and general well-being. A few authors report that the spinal cord symptoms also are markedly improved. In one of our cases with pronounced cord symptoms, although the general symptoms and blood-picture improved, the cord symptoms remained unaltered.

In the clinic of Kuttner, Lewenberg, and Gotthil the effect of liver treatment on achylia was studied. Out of 12 cases, they

found that in only one was there a slight return of the hydrochloric acid. Of the other 11, gastric achylia persisted. They studied the effect of liver treatment on the colon bacilli in the small intestines by means of the duodenal tube. They found that neither the number nor the toxicity of these organisms is diminished under the treatment. They, like most authors, did find, however, that the blood-picture, the subjective symptoms, and, in one case, the spinal cord symptoms, improved markedly, tending to prove that the colon bacilli are secondary invaders.

Congenital Hemolytic Icterus

If this affection gives rise to symptoms and repeated periods of blood crisis splenectomy becomes necessary and is most efficient in bringing about a cure. In successful cases the anemia disappears, the general condition of the patient improves, the urobilin and urobilogen in the urine disappear, and the icterus index becomes normal. The fact that the resistance of the red blood-cells to hypotonic salt solution does not change materially after splenectomy demonstrates that their quality has not been changed, but that the destructive agency has been removed. This tends to prove that hemolytic icterus is a disease of excessive destruction of red blood-cells by the spleen (hypersplenia Eppinger). In the course of hemolytic icterus biliary colic may be the most troublesome symptom, and a cholecystectomy may have to be performed long before splenectomy. After the cholecystectomy the patient may have periods of well-being, and splenectomy may be unnecessary.

A case worth mentioning is that of a lady physician who was afflicted with the disease since earliest childhood. Until she was thirty years of age, it presented very few symptoms. Then severe biliary colic set in necessitating cholecystectomy, which was done by Dr. Blake successfully. A few years later she began to have active symptoms of hemolytic icterus with recurrent attacks of blood crisis. As she did not respond to repeated blood transfusions by Dr. Rosenthal, the late Dr. Brill, Dr. Rosenthal, and others, agreed with us, advising splenectomy, which, unfortunately, terminated fatally.

Banti's Disease

If splenectomy is to have a beneficial effect in this affection, it must be undertaken before the stage of ascites or very severe bleeding sets in.

Gaucher's Splenomegaly

Should this condition give rise to symptoms, splenectomy is the only efficacious method of treatment.

Polycythemia

At most, polycythemia may be treated symptomatically. Lacto-vegetable diet, with the addition of large quantities of fruit, is beneficial. Water may be allowed in sufficient quantities. Alcohol, tobacco, and salt must be excluded, particularly in hypertensive cases. Repeated venesection has been advised by some. This often has a beneficial, although transient, effect. Some authors advise *x*-ray treatment of the spleen and long bones. Mosenthal and a few others have found it very beneficial. Turk suggested the use of drugs which would destroy the red blood-cells, and advised large doses of arsenic. Others have advised benzol; Eppinger, toluylendiamin. None of these drugs has stood the test. Eppinger also advises phenylhydrazin, beginning with 2 c.c. 1 per cent. solution, increasing the dose gradually to 5 or 7 c.c., later a 2 per cent. solution in similar doses, and still later a 5 per cent. solution. In some of the cases a reduction of red blood-cells from the original 8,900,000 to 3,600,000 was obtained. Favorable results with phenylhydrazin treatment have also been reported in New York from many clinics, and from the Mayo Clinic, usually administered in doses of 0.2 gram, increased until 2.4 grams are taken, when it is discontinued. We saw a case in Berlin which, although treated with phenylhydrazin by the Eppinger method, developed yellow atrophy of the liver three days later, and at autopsy the parenchyma of the liver was seen to be destroyed. The method is not safe by any means, and if employed at all, should be commenced with the smallest doses possible. If the slightest discomfort in the liver region is experienced, the treatment should be discontinued.

Leukemias

For acute leukemia there is no treatment. Chronic lymphatic and myeloid leukemias yield favorably to *x*-ray treatment, which may bring about a long period of remission. After a time, however, the symptoms recur with greater severity, and, during this stage, *x*-ray is of no benefit, and may be harmful.

A word of precaution may be warned as to excessive treatment in such cases, and mention may be made of a case of chronic myelogenous leukemia that had been treated on the outside by radium by a physician, and after being admitted to this hospital had died within twenty-four hours. When puncturing several areas over the abdomen at postmortem the needle met with great resistance and pure blood was obtained, illustrating that the entire tumor mass was of the spleen.

Hodgkin's Disease

The treatment of Hodgkin's disease is unsatisfactory. Some cases improve with large doses of arsenic. In the majority, however, remission is brought about by *x*-ray treatment. The cases yielding least to treatment are those where the abdominal glands are most involved. Here the disease progresses rapidly, irrespective of the form of treatment.

Thrombocytopenia

Splenectomy is the only effective method of treating the fulminating type of thrombocytopenia. It should not be delayed unnecessarily, and should be followed by one or more blood transfusions. It is not essential to give a blood transfusion before splenectomy, and such a procedure may be harmful, as pointed out by Rosenthal and Brill, because it may increase oozing from the capillaries, thus causing more bleeding. There is no reason to hasten splenectomy in mild cases, many of which will improve under the ordinary symptomatic treatment: vitamin-rich diet, calcium chlorid, 10 c.c. 5 per cent. solution intravenously, or calcium lactate by mouth. Large doses of iron, also, should be given. Foreign proteins intramuscularly have been advised by some as well as *x*-ray treatment over the

spleen and long bones. We do not know of any objection to *x*-ray treatment over the long bones, but it is certainly to be discouraged over the spleen because, if there is to be a later splenectomy, the adhesions caused by the *x*-ray treatment increase the difficulty of operation.

We appreciate that in discussing this vast subject of hematologic diseases we have, of necessity, been fragmentary from a scientific standpoint, but from the clinical point of view we have made an effort to omit nothing of actual practical value.

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CLINIC OF DR. PHILIP MOEN STIMSON

A Report of the Floating Hospital of St. John's Guild of New York City for the Summer of 1927

"A QUARTER OUNCE GAIN PER BABY PER DAY"

The Floating Hospital Ship, Helen C. Juillard, is a familiar sight to the marine workers of New York Harbor. With its decks filled with gossiping mothers, romping children, and

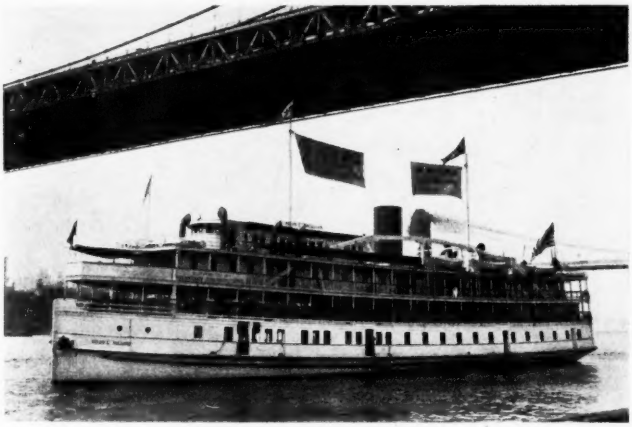


Fig. 139.—The floating hospital.

squawling infants, and always with a sailor in a rowboat hitched at the stern on the watch for a youngster overboard, it has been seen by countless travelers on incoming or outgoing ocean liners, and on the harbor ferries. But its work is little known in medical circles even in its own city of New York. And now that the Boston Floating Hospital is still without a floating home, its former boat having been destroyed by fire in 1927, the

Fig. 140.—Staff of the boat: Front row, nursemaids; second row, nurses; third row, playground workers, captain, superintendent, interns, housekeeper, kitchen help; rear, firemen, crew, cooks, etc.

Fig. 141.—Well enough to go home.

Fig. 142.—A sun bath on the bow deck for babies on the "white service" in the ward.

Fig. 143.—Free milk for lunch.

Floating Hospital of St. John's Guild is the only hospital of this type in the United States. Accordingly, in order that the medical

Fig. 144.—At the afternoon clinic for the day-trip babies.

Fig. 145.—The milk booth. Bottles for babies twice a day.

public may know something of its work in its unique field, there follows a brief description of the hospital, its scope, and its methods.

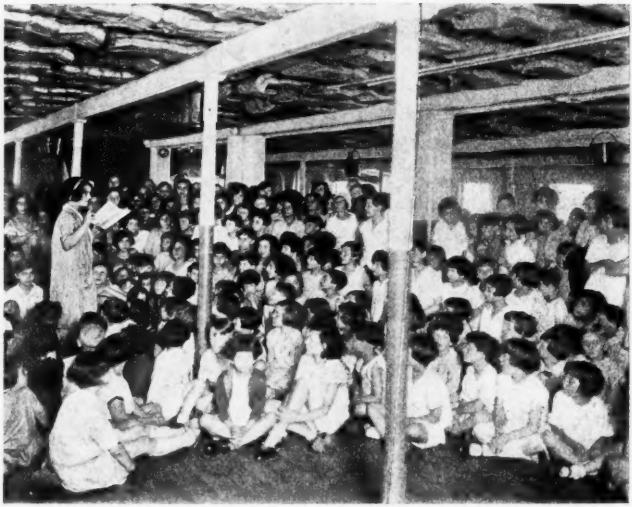


Fig. 146.—The girls' turn on the play deck. Story hour.

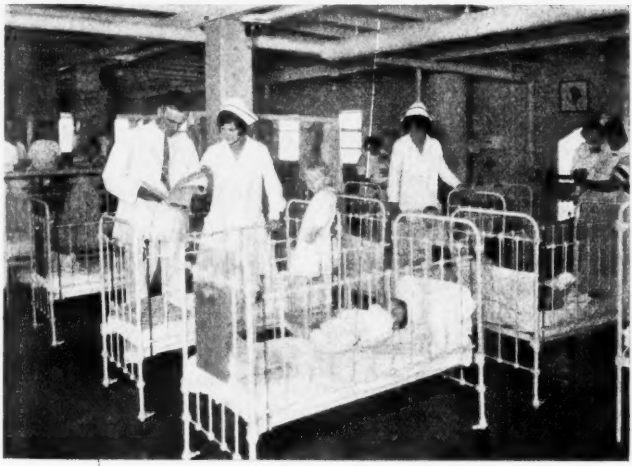


Fig. 147.—In the ward, the white service.

There is also another reason, however, for presenting particularly the work of the ward or overnight service. In 1927

our babies of all types of trouble made an average net gain of ¼ ounce per baby per day while in the ward. In the belief that this was a good record, search was made for similar records from other hospitals so that there might be a comparison, but none have been found. It is, therefore, hoped that after reading this report pediatricians in other baby hospitals may find it of interest to combine their results obtained in all infants admitted in July and August and compare them with those of the Floating Hospital, given herewith. True it is that it may seem almost impossible to find analogous conditions, such as types of

Fig. 148.—Showers and tubs, one side of the bath-room.

illness, age of infants, kind of weather, but surely conditions may be somewhat approximated by taking gross averages. The staff of the Floating Hospital of St. John's Guild would like to know if its record is good or poor; if there are advantages for sick babies in a hospital on the water, or had these babies better stay on land.

As to equipment, the work of the Floating Hospital of St. John's Guild is in two parts, namely: The ward or overnight service, and the day-trip service. For the former, there is a beautifully equipped ward of thirty cribs on the third deck,

with two dressing rooms, a diet kitchen, sterilizing room, and clinical laboratory; also two isolation rooms and an admitting room. For the day service there are on the lower two decks benches seating nearly twelve hundred mothers and children, a considerable play space, and a bath-room containing about forty tubs and showers. There is also a bench area on the third deck used for special groups, such as the patients attending the afternoon clinic held by the interns. The stern part of each of the three decks and much of the top deck is used for staff quarters, office, kitchen, stores, toilets, etc. There is no automotive power—a tug being used for towing.

The small size of the ward service has not seemed to warrant the addition of *x*-ray equipment, especially since members of the visiting staff have always been able to have absolutely necessary *x*-ray work done through the courtesy of neighboring hospitals with which they have connections. Similarly there are no facilities for elaborate blood chemistry and other quantitative analyses; but there are adequate facilities for routine clinical analyses and for such ward treatments as transfusions and infusions, these latter helps for dehydrated and other babies being frequently resorted to.

About the day service, but little need be said here. It is intended for giving mothers and little children a day on the harbor away from the heat of the city streets. Free milk and bread and butter are given each family, and infants are supplied according to the accompanying scheme (Chart 2) with bottles of formula milk that are roughly suitable to their individual needs. Two trained kindergartners organize the play of groups of children on the lowest deck, a bath-room nurse supervives the bath-room, and a health-worker does what health education work she can do with practical demonstrations and assists the two interns with their daily afternoon clinic. At this clinic the work is largely diet regulation, the treatment of minor troubles, and referring patients for operative and other matters to the various land clinics and hospitals of the city.

Statistics for the day service for the past four years are as follows:

CHART 1

	1924	1925	1926	1927	1928
Mothers	14,094	9,589	6,901	7,687	9,011
Children	32,903	25,752	19,994	20,251	26,584
Babies	7,473	4,308	2,775	4,549	3,088
Total	54,470	39,649	29,670	32,487	38,683
Number of trips made	50	45	42	47	51
Average per trip	1,089	881	706	691	759
Number of baths given	12,810	8,560	9,114	13,517	13,089
Percentage of total receiving baths	23.6	21.5	30.1	41.6	33.8
Attendance at deck clinic	657	616	376	816	1,319
Average daily attendance	13	13.7	9	17.4	25.9

The total number carried in 1926 and 1927 is much lower than in previous years because of a comparatively small number of excessively hot days, and especially because of a lowering by the Board of Directors of the total number allowed on a trip—from 1600 to 1200—in the belief that too great crowding counteracted much of the benefit of the trip. On the other hand, and perhaps as a result, there were gratifying increases in 1927 in the use of the clinic and of the baths.

The overnight or ward service is presumably similar in most respects to that of any summer hospital for infants. There are thirty cribs, of which about twelve are in glass enclosed cubicles. In 1927 there were in all 53 admissions for a total of 1272 nights treatment or an average stay per baby of 24 nights.

CHART 2

DAY-TRIP SERVICE—BOTTLE FORMULAS

Mixture A		*Mixture B*	
Boiled whole milk	10 oz.	Boiled whole milk	15 oz.
Water	20 oz.	Barley water	15 oz.
Milk-sugar	2 level tbsp.	Milk-sugar	3 tbsp.

Mixture C		*Mixture D*
Whole milk (unboiled)	20 oz.	Whole milk (unboiled)
Barley water	10 oz.	
Milk-sugar	3 tbsp.	

Weight.	Age: Two to four weeks.	One month.	Two months.	Three months.	Four months.	Five months.	Six to seven months.	Eight to nine months.	Ten to twelve months.	One year and over.
5–6 lbs.	A-2									
7–8 lbs.	A-2½	A-3[1]	B-3							
9–10 lbs.	...	A-4	B-4	B-5	B-5					
11–12 lbs.	...	...	B-5	B-5	B-5	B-6				
13–14 lbs.	...	...	...	B-6	B-6	C-6	C-7	C-7		
15–16 lbs.	...	...	...	...	B-7	C-7	C-7	C-8	C-8	D-8
17–18 lbs.	...	...	...	...	...	...	C-8	C-8	C-8	D-8
19–20 lbs.	...	...	...	...	...	...	...	...	D-8	D-8

[1] A-3 signifies 3 oz. of Mixture A.

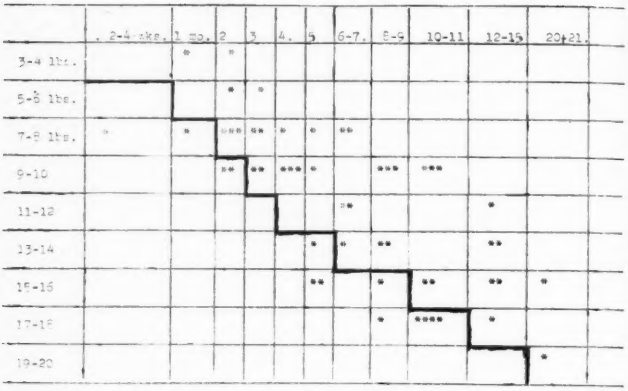
Babies whose weight- and age-square is within the area above the heavy line should be referred to the health-worker and the 2 P. M. Clinic.

The great majority of the babies (40) suffered from malnutrition as is shown in Chart 3, "Admission Weights." Acute alimentary disturbances of more or less severity were present in 22 cases including 3 cases of acute intestinal intoxication. Rickets sufficient to be of clinical significance was found in 8 cases, and there was a marked case of scurvy, curiously enough involving even the spine. There was one case each of pylorospasm, birth injury (Still's disease), congenital malformation of the heart, and eczema; and 3 of prematurity. Infections included 12 cases of otitis media, 6 of bronchitis, 4 of pyelitis, 3 each of pharyngitis and of furunculosis, and one each of specific vaginitis, pertussis, and diphtheria carrier. There was also a contact to tuberculosis, and 6 so-called boarders, or well babies, taken for diet regulation and training.

There were two deaths in the hospital, and a third shortly

CHART 3

Admission Weights, Season of 1927



after transfer to another hospital, the transfer being necessitated by the close of our season. Four other babies were transferred to other hospitals, three because of contagious disease, and one because the end of our season came before the child was fit to go home. Six were taken home during the season against advice, before we were satisfied with the children's condition. The remaining 40 were all cured or sufficiently improved to be discharged home on simple formulas and with a good prognosis.

While on the boat, 14 babies lost a total of 125 ounces, of which the 3 that died accounted for 62 ounces. Five made no change in weight, and 34 made a total gain of 452 ounces. Therefore, the 53 babies made a total net gain of 327 ounces in 1272 nights, or an average gain of $\frac{1}{4}$ ounce (0.257) per baby per day. The only figures with which we have been able to compare this are from our own hospital when during the season of 1925, 57 babies made a net gain of 171 ounces in 877 nights, or about $\frac{1}{5}$ ounce (0.195) per baby per day. The figures for the rest of the babies of that season are not available.

Thirteen babies at one time or another had protein milk;*

* For descriptions of these types of formulas see a symposium on Infant Feeding in the Archives of Pediatrics, vol. xlii, No. 11, November, 1925.

21 acidified lactic acid milk; 10 cultured lactic acid milk, prepared on the boat; 5 thick cereal formulas; and 2 breast milk. There were 6 instances where more complicated formulæ were tried. Sixteen babies received no other milk than a simple sweet milk formula, but most babies received two or more different types of feeding. Chart No. 4, while based on too few

CHART 4

	Patients combined.	Patients with otitis.	Patients without otitis.
Simple milk formula:			
Number of infants	21	6	15
Days, total	293	144	149
Ounces gain or loss	+75	+30	+45
Ounces per day	0.257	0.208	0.302
Acidified lactic acid milk:			
Number of infants	21	2	19
Days, total	310	26	284
Ounces gain or loss	+92	+2	+90
Ounces per day	0.296	0.076	0.316
Cultured lactic acid milk:			
Number of infants	10	3	7
Days, total	184	34	150
Ounces gain or loss	+116	+28	+88
Ounces per day	0.630	0.823	0.586
Thick cereal:			
Number of infants	5	2	3
Days, total	63	20	43
Ounces gain or loss	+34	−1	+35
Ounces per day	0.539	.....	0.813
Total comparison:			
Number of infants	.....	13	44
Days, total	.....	224	626
Ounces gain or loss	.....	59	258
Ounces per day	.....	0.263	0.410

babies, and too variable conditions for any accurate deductions, is nevertheless of interest in showing our impression of the general relative efficacy in weight production of four different types of feeding, and particularly the effect of the presence of otitis

media in lowering the tendency to gain in weight. Cereal, broth, and vegetables were added to the menu when possible, and nearly all babies received orange juice and cod-liver oil.

Only one illustration of the problem-cases of 1927 will be given. One patient was admitted weighing 3 pounds, 10 ounces at six weeks of age. She was fed half on bottles of breast milk —all that was obtainable each day—and half on an acidified lactic acid milk formula. When discharged, aged twelve weeks, on a simple lactic acid formula which the mother could easily prepare, she weighed 5 pounds, 15 ounces, or a gain of 37 ounces in forty-five days. Her breast milk cost the hospital a little over $50.00.

Because the hospital is away from its pier each week day from 9 A. M. to 5 P. M., "rounds" have to be made at the end of the afternoon. Each Wednesday at five, "grand rounds" are held at which all members of the staff are expected to be present and to which visiting doctors are welcomed. The salient features of each case are brought out and the reasons for success or failure in the treatment are discussed. Four associate attending physicians divide the other daily 5 P. M. rounds, two being on duty each of the two months of July and August when the boat is in operation. Each doctor makes rounds Sunday, Tuesday, and Friday of one week, and Monday, Thursday, and Saturday of the next; thus alternating nights or week-ends with the other pediatrician on duty. The first attending physician to see a new patient has the general supervision of that case while it remains in the hospital, and a suitably colored disk is pasted on the front of the patient's chart to show to which attending physician it belongs. There are two resident interns who divide the work equally, taking the admissions alternately, and each doing all the work of his own patients under the supervision of the attendings. As a result, an intern has about half his patients with each of the two attending physicians on duty, and his charts are also marked for easy identification as by a colored star.

All new cases are admitted into isolation cubicles and kept there under aseptic technic until proved free from infection when

they are moved out into the open center of the ward. As a result of this precaution, in 1927, 3 cases of contagion (whooping-cough, specific vaginitis, and diphtheria carrier) were in the ward 24, fourteen and four days respectively without any secondary cases ensuing. On the other hand, 7 of the 12 cases of otitis media were apparently contracted on the boat from exposure either to the other 5 such cases, or to the 6 cases of bronchitis and 3 of pharyngitis. Chart 4 has already illustrated the deleterious effects of otitis media on weight production.

Accordingly, to cut down still further the dangers of such parenteral infections, it is planned for the season of 1928, to divide the patients and nurses into three services: a red service composed of those babies known to have some infection and therefore dangerous, a white service where the infants are believed to be free from infection or "pure," and a blue service of new cases or others about which there is still uncertainty. Nurses will wear arm bands to denote their service and will not be allowed to touch a baby on another service except under unusual circumstances and with unusual precautions. Babies on the red service will be on the strictest aseptic technic and will not leave their cubicles. A special dressing room will be used only by the white babies and their attendants, but there will be no individual isolation on this service which it is hoped will be the largest. Another dressing room will be available for such of the babies on the blue service as appear to be safe; the others being confined to their cribs under aseptic technic. It is hoped that by this means the intercommunication of upper respiratory and other infections will be minimized.

Such, in brief, is the work of the Floating Hospital of St. John's Guild. To counteract the many disadvantages of lack of diagnostic facilities, of awkward hours of accessibility, and of a short season, the babies on the ward service have had the advantages of comparatively cool days, of skilful nursing, and enthusiastic tireless interns. A quarter ounce per baby per day is the result for 1927.

CLINIC OF DR. EDMUND H. HUBNER

DEPARTMENT OF OBSTETRICS OF THE FIFTH AVENUE HOSPITAL

THE PROBLEM OF THE PREMATURE INFANT

THE premature infant remains one of the most troublesome problems in the practice of obstetrics and pediatry. This article offers some practical suggestions in the care of these infants and gives a brief description of an incubator that is in marked contrast to those of earlier design. Its simplicity of construction and operation makes it easily accessible for use in any hospital nursery.

While the object of this paper is not to introduce something new, we do wish to emphasize some of the measures now being used in the care of premature infants at the Fifth Avenue Hospital. These measures which are being used with uniformly good results in the management of our prematures may be grouped under the following headings: (1) Maintenance of a moist, equable body-temperature; (2) prevention of a dehydration; (3) protection from infection; (4) breast milk.

1. The maintenance of a moist, equable body-temperature is obtained in a specially constructed incubator of rather new design, which was first called to our attention and tried out at another hospital with which this service has connection.

This incubator is a large box, open at the top and bottom, made of light box-wood or composition. Its dimensions are as follows: Height, 3 feet; width, 2 feet; length 2½ feet. It is raised approximately 2½ inches from the floor by casters, which allow cool, fresh air to pass in, and there is also a series of perforations, five on a side, 2½ inches in diameter, located near the bottom of the incubator, which also permit the entrance of cool air.

The heat is generated by four 60-watt electric light bulbs, one located in each corner near the bottom of the incubator so that air, on entering, is equally warmed and circulates freely within the incubator absorbing moisture before rising to the level of and enveloping the infant's crib. A large shallow pan for water rests on a framework close to the bottom of the incubator between the four heat-generating bulbs.

Fig. 149.—Side view of incubator.

The infant's crib is suspended within the incubator below the level of the top border and is protected from drafts at all times. This suspension allows a free passage of warm, moist air around the four sides and the bottom of the crib, as there is a space of $2\frac{1}{2}$ inches between the sides of the crib and the sides of the incubator.

A thermometer is kept in each infant's crib and frequent

readings are made to keep the temperature of the incubator between 97° and 99° F.

The heat generated by the bulbs gets its moisture from the pan of water above described, and rising in the incubator, is arrested at the crib for the use of the infant, by blankets thrown across the top of the incubator over the crib. One of these blankets is at the foot and one at the head, so that only the infant's head and face are exposed.

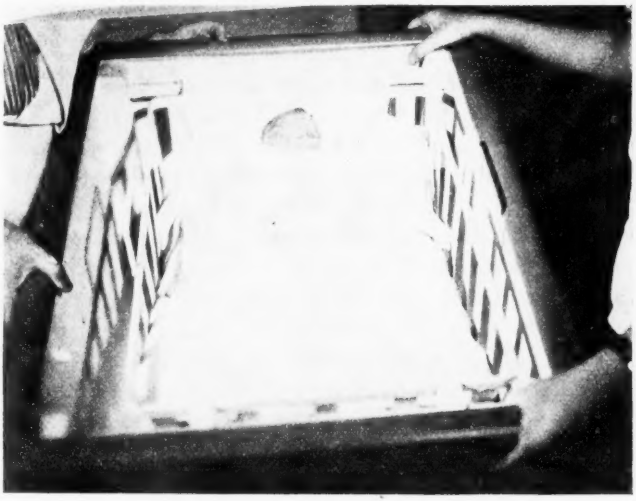


Fig. 150.—Top view of incubator looking down.

The bulbs are controlled by a conveniently located four-way switch, which allows perfect control of one or all bulbs without making it necessary to remove the crib, pan of water, or insert the fingers through the ventilating holes. The number of bulbs that must be lighted to maintain the incubator at the desired temperature is governed largely by the temperature of the room.

2. The prevention of dehydration is a most important item, for as many premature infants die from dehydration as from starvation. We try with marked success, to prevent this in three ways:

(*a*) By moistening the air coming in contact with and breathed by the infant, as described above in detail.

(*b*) By hypodermoclyses of a 5 per cent. solution of glucose in normal saline. These injections are given as frequently as needed to keep the skin moist and smooth. From 40 to 50 c.c. are given at one time in two injections of from 20 to 25 c.c. usually in each thigh, buttock, or the scapular or mammary region. Different locations for these injections must be chosen to prevent infection, to allow time for complete absorption and healing, and to prevent irritation with subsequent induration.

(*c*) These babies are oiled, not bathed, to prevent as far as possible, the evaporation of moisture from the skin.

3. Freedom from infection is striven for by special nursing care for the premature infants in the nursery. A special nurse is in attendance on these babies and we hope soon to have a separate room for them. In the meantime they are carefully protected by the immediate removal from the nursery of any infant contracting an infection or developing any fever that may be regarded as possibly of infectious origin.

These infants are disturbed or moved from their cribs as few times during the day as possible. They are not taken to the mothers' room for nursing nor fondling, nor are they exhibited to relatives or other visitors. The parents are given to understand that in order to be given its best chance for survival, their premature baby must not be disturbed and must remain in the hospital until it attains a weight of at least 5 pounds before it may be discharged.

4. The question of feeding is, of course, of paramount importance and remains the most difficult of all problems in the care of prematures. In spite of every possible scientific aid in the artificial feeding of these babies, no formula no matter how simple nor how elaborate can successfully compete with breast milk. In the 5 cases reported herewith, whenever a baby lost, ceased to gain or gained but poorly, it was during a dearth in the supply of breast milk.

The supply of breast milk by patients in the hospital is a most uncertain quantity, but in this regard we would like to

emphasize two things that have helped us materially to obtain a rather even supply of breast milk from patients as needed. One is the great convenience of the electric breast-pump, the use of which is not discomforting to the nursing mother, and in painfully engorged breasts, often is welcomed by the patient as a source of relief. Besides its great convenience, its speed, and its lack of discomfort, it very often acts as a galactagogue. One of the most reliable ways to create a sufficient supply of breast milk or to continue an already sufficient quantity, is to empty the breasts, and this the electric breast-pump certainly accomplishes.

Another important factor in keeping a more or less constant available supply of breast milk is the previously acquired knowledge that the mothers in the hospital who have milk to spare, have no constitutional drawback or chronic disease, so that their milk may be a fit food. For this reason all staff patients are given a thorough physical examination, a most careful history is taken, and the Wassermann test is made routinely.

The following 5 case-reports are presented in support of the treatment as above outlined. These babies were all premature, weighing less than 4 pounds at birth and in two instances the initial loss of weight and subsequent losses caused the weights of the infants to fall below 3 pounds. All were treated successfully by the above mentioned method, although these particular cases proved to be rather more difficult than the average run of prematures.

The last case especially, baby S. R., is of particular interest for in this case artificial feeding was attempted between feedings of breast milk, which proved to be rather scarce at the hospital during this baby's early days. He would cease to gain or would gain but poorly on butter soup, lactic acid milk, concentrated or diluted formulæ, boiled, raw or powdered milks, etc., but when fed breast milk he would begin an almost immediate improvement. This baby is still in the hospital and thriving most satisfactorily on our present rather plentiful supply of breast milk.

Case I.—Baby M. D. Born July 23d. Weight at birth 3 pounds, 12 ounces. Two and one-half months premature. Cause of prematurity was pre-eclamptic toxemia of mother. Initial loss of weight, 6 ounces in six days. Baby was started immediately on a formula of half breast milk and half water, but it has been brought home to us that the initial loss of weight cannot be

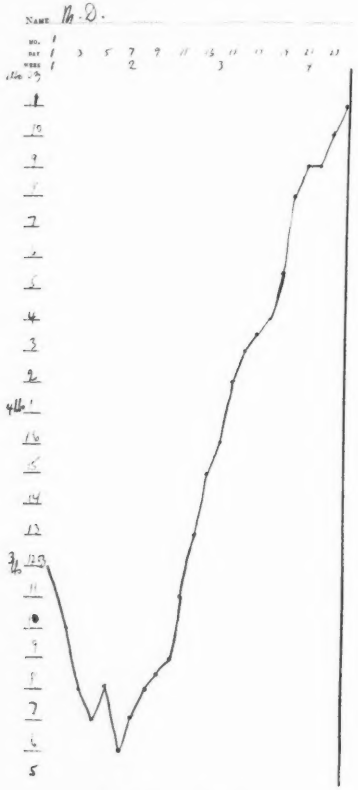


Fig. 151.—Case I.

prevented entirely. Full term infants as well as prematures will lose weight during the first three or four days of life in spite of every measure that may be taken to prevent it. During these first few days of life most infants nurse poorly or tolerate very poorly whatever food is given them. This initial loss may be controlled, but not prevented.

Discharged August 24th. Weight on discharge 5 pounds, 6 ounces.

Case II.—Baby J. C. H. Born December 18th. Birth weight, 3½ pounds. Ten weeks premature. Cause of prematurity was pre-eclamptic toxemia and nephritis. Initial loss of weight 8 ounces in four days. Breast milk from birth.

Fig. 152.—Case II.

Discharged February 1st. Weight on discharge 5 pounds, 4 ounces.

Case III.—Baby E. R. Born December 2d. Birth weight, 4 pounds 9 ounces. Six weeks premature. Cause of prematurity, trauma with pre-

mature rupture of water-sac. Initial loss of weight 9 ounces in four days. Breast milk from birth.

Discharged February 6th. Weight on discharge 6 pounds, 6 ounces.

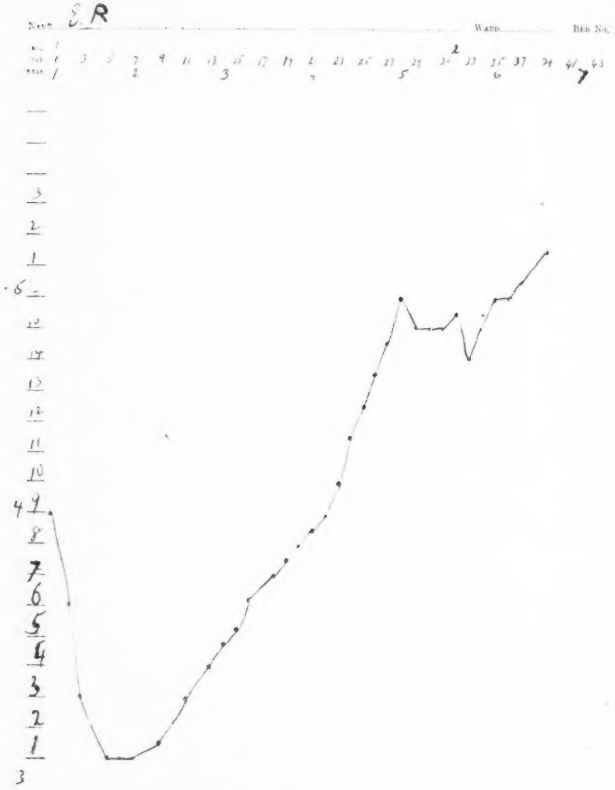


Fig. 153.—Case III.

Case IV.—Baby M. S. Born August 11th. Birth weight, 3 pounds, 7 ounces. Nine weeks premature. Cause of prematurity not known. Initial loss of weight 7 ounces in four days. Breast milk from birth.

Discharged September 14th. Weight on discharge, 5 pounds.

In this case the mother, after leaving the hospital, rented her own breast-pump; pumped her breasts at home and sent the milk in. Where patients

cannot afford this, they are instructed to report at the hospital once or twice a day for pumpings.

Fig. 154.—Case IV.

Case V.—Baby S. R. Born April 6th. Birth weight, 3 pounds. Ten weeks premature. Cause of prematurity rupture of amniotic sac. Initial loss of weight, 8 ounces in four days. Breast milk from birth. Weight remained stationary for seven days after the initial loss and then dropped to 2 pounds, 6 ounces while various formulæ were being tried, owing to the scarcity of breast milk. Upon return to breast milk the baby began to gain, and is now 3½ pounds. He is five weeks old and is thriving, gaining almost an ounce a day.

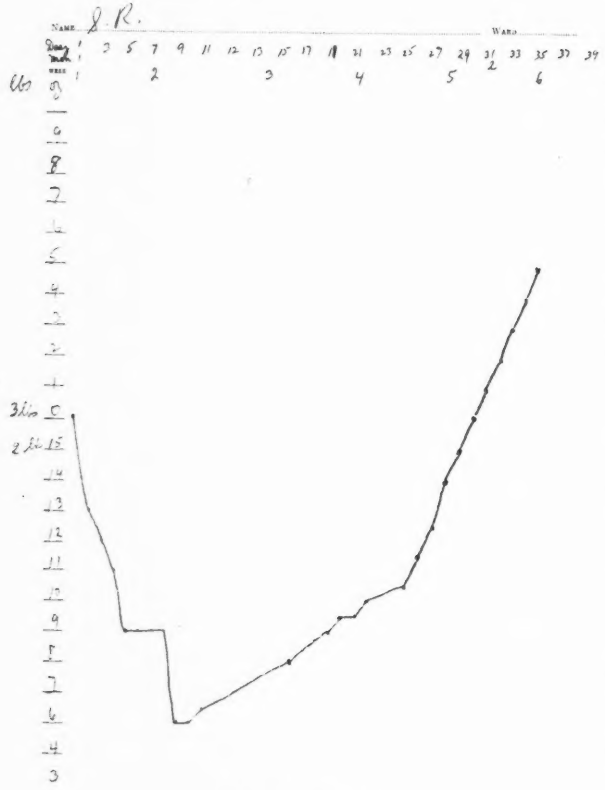


Fig. 155.—Case V

CLINIC OF DR. RALPH G. STILLMAN

DIVISION OF LABORATORIES, NEW YORK HOSPITAL

AGRANULOCYTOSIS

I WISH to present today for your consideration the records of 2 cases seen some time ago at the New York Hospital.

Case I.—The first patient was an unmarried girl of nineteen who had had an acute infectious disease, nature unknown, at the age of thirteen. She had been subject to attacks of tonsillitis, and her tonsils were removed when she was fourteen. About three months before we saw her she had a brief attack of conjunctivitis, and at about that time it was noticed that she was losing her natural color. Seven weeks before coming to this hospital her throat became sore and she entered another hospital where a diagnosis of acute tonsillitis and conjunctivitis was made. A peritonsillar abscess developed and ruptured, and after a stay of two weeks she returned home improved.

She regained her strength slowly and soon began to have trouble again with her eyes. Her ankles swelled at times and she had trouble in urinating. Dyspnea appeared and her pallor increased, and finally her physician was able to persuade her to enter the hospital. She was admitted to the Service of Dr. L. A. Conner.

On admission her temperature was 102.6° F. and pulse 122. There was noticed marked pallor of the skin, photophobia and some injection of the conjunctivæ. The lungs were negative, and the heart negative except for a soft systolic murmur heard at the mitral area. The liver was slightly enlarged and the spleen palpable, but the superficial lymph-nodes could not be felt. Ophthalmoscopic examination revealed scleritis, marginal keratitis, and seborrheal blepharitis thought to be due to a simple infection. Wassermann reaction negative. The urine showed only a few pus-cells. The blood-urea nitrogen was 12 mg. per 100 c.c., and a blood-culture was sterile.

A blood count showed 1,300,000 red cells with 20 per cent. hemoglobin. The white cells were only 1000, and the differential count showed only 21 per cent. of polymorphonuclear neutrophils. Lymphocytes were 76 per cent., Turk's irritation cells 2 per cent., large mononuclears none and a single myeloblast. The red cells showed moderate anisocytosis, slight polychromatophilia and some poikilocytosis. Some large cells were seen but no nucleated or stippled erythrocytes. At that time it seemed that the patient might be suffering from what has been called aplastic anemia, except that she had none of the hemorrhages usually seen in that disease.

During her stay in the hospital her temperature varied between 101° and 105.8° F., being in the neighborhood of 104° F. the greater part of the time. A transfusion of whole blood served to raise the red cells to 2,300,000, but the white cells remained unchanged between 1000 and 1100. The neutrophils varied between 19 and 35 per cent. A single nucleated red cell was found on one occasion. The platelets were 100,000. She improved slightly for a time and then gradually failed. On her sixteenth day in the hospital she passed some blood by rectum and a few petechiæ were found along both clavicles. On the eighteenth day signs of consolidation were found in the lungs, and she died early the following morning.

At no time during her stay in this hospital was the condition of her mouth such as to attract attention. The teeth and gums were in good condition, and evidence of her recent tonsillitis and peritonsillar abscess had almost completely disappeared. Only by careful examination could one detect any deviation from the normal, this consisting of slight redness of the mucous membrane.

Autopsy was performed four hours after death. There was recognized moderate edema of the feet and legs. The subcutaneous fat was golden yellow. There was consolidation in the posterior portions of both upper and lower lobes of the left lung. In the upper lobe there was a small necrotic area that was interpreted as a beginning gangrene. The spleen was twice the normal size and showed only congestion and some diminution in the amount of lymphoid tissue. No source of hemorrhage was discovered in the intestinal tract. There were petechial hemorrhages beneath the mucosa of the pelvis of both kidneys and of the bladder. A film made from marrow expressed from a rib showed a remarkable scarcity of cells of the myeloid series. It was estimated that less than 1 per cent. of the cells were polymorphonuclears and there were but few myeloblasts. A single somewhat doubtful normoblast was seen. The picture was that of an aplastic marrow.

Cultures from the heart blood and from the pus in the gangrenous focus in the lung yielded a pure growth of the Bacillus pyocyaneus.

Case II.—The second patient was an unmarried man of thirty, a truck driver with a negative previous history, who came to the New York Hospital with the story that some ten days before, his dentist had told him his gums were swollen. Two days later his gums began to bleed and his throat became sore. Hemorrhage from the nose and mouth had become severe, and he felt weak and feverish when he came to the hospital. He was admitted to the Service of Dr. William R. Williams.

On admission, his temperature was 105° F., pulse 96. The mucous membranes of the nose, mouth, and pharynx were swollen, purplish and congested, and bled easily. There was an ecchymosis on the soft palate, and the breath was foul. The lungs were negative, the heart showed a soft systolic murmur at the apex and the abdomen was negative. The superficial lymph-nodes were not enlarged. There were purpuric spots over the abdomen and extremities. On the day of admission, the blood showed 2,700,000 red cells, 45 per cent. hemoglobin, and 1500 white cells. *No polymorphonuclears* were found in the stained film. Two days later the white cells were 900 with 6

per cent. polymorphonuclears and on the next day the white cells were 500 and the polymorphonuclears 3 per cent. The mononuclear cells were chiefly small lymphocytes that appeared to be quite normal. A few large mononuclear cells were the subject of some discussion, but it was finally agreed that they probably should not be interpreted as lymphoblasts. The platelets were 48,000, icterus index 17, coagulation time nine minutes, bleeding time one minute, and the osmotic resistance of the red cells normal. A blood-culture showed a Type II pneumococcus. Wassermann reaction and urine were negative. On the second and again on the fourth day of his stay in the hospital he was given transfusions of 500 c.c. of whole blood. The bleeding stopped after the second transfusion. His temperature remained steadily between 105° and 106° F., he became delirious and on his fifth day in the hospital his temperature rose to 107° F., and he died.

Autopsy was performed two hours after death. There were numerous petechiæ in the skin. There was consolidation of the middle lobe and portions of the upper and lower lobes of the right lung, and some irregular consolidation in the left lung. Microscopic examination showed practically a complete absence of polynuclear cells in the exudate, and the lesion was interpreted as an unresolved pneumonia. The liver, spleen, and lymph-nodes presented no significant changes. The bone-marrow was not examined. Blood-culture taken at autopsy yielded a growth of Bacillus coli communis and B. pyocyaneus.

These cases are well marked instances of leukopenia with extreme reduction in the number of granular cells, but present certain differences. In the first case there was almost complete absence of hemorrhagic symptoms, the platelets were not affected and there was no lesion in the throat, though infection of the tonsils had been present a short time previously. In the second case hemorrhagic symptoms were prominent, the platelets were definitely reduced and there was severe involvement of the throat and mouth. In both cases there was anemia, the fever was high, and the illness appeared to be fundamentally an infection. Both patients died with pneumonia and in both the Bacillus pyocyaneus was recovered from the blood at an autopsy performed a few hours after death.

Marked reduction in the number of granular cells in the blood is found in aplastic anemia or aleukia hemorrhagica, idiopathic purpura hemorrhagica or essential thrombocytopenia, chronic benzol poisoning, agranulocytosis or agranulocytic angina, and in some instances, of bacteriemia without involvement of the throat and mouth. The first case resembles agranulo-

cytic angina except that the throat symptoms disappeared before the change in the blood-picture was discovered, and there was severe anemia. The high platelet count excludes essential thrombocytopenia, the absence of hemorrhagic manifestations weighs against a diagnosis of aplastic anemia, and a blood-culture was sterile during life. The second case suggests idiopathic purpura hemorrhagica except that the reduction in the granular cells is more marked than is usually seen in that condition. The anemia was not as severe as is usually seen in fatal cases of aplastic anemia. The finding of the pneumococcus in the blood-culture was probably associated with the pneumonia which was apparently a terminal process. In neither case was there any reason to suspect benzol poisoning. In both cases the findings at autopsy excluded the possibility of acute leukemia. In both cases there was marked fever and the Bacillus pyocyaneus was recovered from the blood at autopsy.

Agranulocytic angina was first described by Schultz in 1922 as an acute condition generally found in young adult females, and invariably fatal, characterized by intense ulceration in the mouth and throat, fever, and extreme reduction in the number of granular cells in the blood. The platelets are not affected, and it is said that the eosinophils may not be reduced in number. Hemorrhages are absent or slight. Anemia is usually not marked and the spleen is somewhat enlarged. Since the first report attention has been directed to instances of leukopenia and a number of atypical cases have been reported. In all of the cases reported there has been noted the presence of symptoms that have led the observer to believe an infection was present even though this infection was at times believed to be superimposed or secondary.

In a surprisingly large number of cases the Bacillus pyocyaneus has been reported. This attracts attention because the perforation is greater than is found in a similar number of autopsies in other conditions. Bacillus pyocyaneus is usually regarded as a relatively non-pathogenic organism. Although it has been found not infrequently in wounds it produces there an infection of chiefly local significance in that it interferes with

healing. It has been reported as causing infections in other regions, but nearly always these are characteristically mild. Lovett's work, however, suggests that when this organism is grown under certain conditions it is able to bring about a certain amount of depression in the leukocyte count, at least in guinea-pigs. Nevertheless, the pyocyaneus has not been found in all cases and other organisms, such as the Staphylococcus aureus and the hemolytic streptococcus, have at times been associated with similar extreme leukopenia.

In reviewing the cases reported since Schultz' first communication, one finds many deviations from the supposed typical picture. The platelets may be reduced, purpura may be observed, the anemia which is typically mild may be severe, and splenomegaly may be present or absent. Cases have been described in males and in a number of instances recovery has been reported. McAlpin has seen one case in which recovery from an attack of apparently true agranulocytosis was later followed by a second attack which proved fatal and Friedman reports a similar case. The less severe cases have resembled what has been called monocytic angina and have presented some points of similarity with "glandular fever" which is almost always a mild condition.

Piney has pointed out that a familial tendency or constitutional predisposition is especially apt to be found in the group of so-called diseases of the blood. This is almost certainly true of pernicious anemia and hemolytic icterus, and there are many features of the group of hemorrhagic diatheses which suggest such a possibility. If such is the case then there must be added to the predisposition an exciting cause which may or may not vary in any one condition. For instance, a pernicious type of anemia develops in only a small percentage of those infested with the Bothriocephalus latus and it is said that these are all of one constitutional type. On the other hand a number of exciting causes have been demonstrated in cases presenting the pernicious type of anemia so that it seems clear that this blood-picture is merely a type of reaction on the part of the hematopoietic tissues, and that true addisonian anemia embraces only

a portion of the patients presenting this reaction. The theory of a constitutional predisposition in agranulocytosis is supported by the history of the case in which recovery was followed by a second and a fatal attack.

In consideration of the above observations the following suggestions may be advanced tentatively until such time as increasing information shall disprove them.

1. Agranulocytosis is a better term than agranulocytic angina since the throat symptoms are not always present.

2. Agranulocytosis is probably related to monocytic angina and glandular fever, and may represent the severe form of those conditions.

3. Agranulocytosis is probably a special form of reaction on the part of the hematopoietic system to infection, rather than the result of the activity of a special infective agent.

4. Agranulocytosis is probably due to the activity of some external stimulus operating in individuals exhibiting a constitutional predisposition.

5. This external stimulus is most frequently some form of infection, and conditions are such that even the Bacillus pyocyaneus may at times play a significant part in the etiology of the condition.

6. The high mortality of the severe forms of the disease is probably associated with the lack of resistance which accompanies marked reduction in the number of granular cells in the blood.

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CLINIC OF DR. F. M. FRANKFELDT

POLYCLINIC HOSPITAL

DIAGNOSTIC METHODS IN DISEASE OF THE RECTUM AND COLON

MEDICAL colleges fail to equip their graduates with a training necessary to interpret pathologic changes in the rectum and colon. Very few hospitals have an established proctologic service, so that the average physician embarks on a medical career without the opportunity of familiarizing himself with the methods of diagnosis in this important field. This failure of medical education coupled with timidity of the patient and a dislike for such examinations on the part of the physician, explain why so many simple complaints of the rectum and colon are overlooked or treated without any attempt at scientific investigation.

Early diagnosis in this region is imperative, otherwise apparently simple conditions become progressively worse, less responsive to attempts at cure, and may even threaten a patient's life. Infections become more extensive, invading deeper structures, a fissure may become infected, form abscess and fistula; thus, a simple adenoma may undergo malignant degeneration. A neglected early carcinoma forms metastasis, and is then inoperable.

It is important to establish a routine procedure when one attempts to interpret pathologic changes in the rectum and colon. The following agencies are at our command:

1. A careful history.
2. General physical examination.
3. Examination of anus, rectum, and colon-
   (*a*) Inspection.
   (*b*) Palpation.
   (*c*) Instrumental.

4. *x*-Ray.
5. Biopsy.
6. Laboratory.

History.—A careful and detailed history is one of the most useful means of arriving at a diagnosis. It should include any facts that might add to the aspects of the case. The following is a form I usually use:

1. Family history:
   Particularly, as pertains to rectocolonic disease, malignancy, tuberculosis, or venereal disease.
2. Previous history:
   (*a*) Medical:
   Tuberculosis, residence in tropics, typhoid, loss of weight, genito-urinary disease, cardiovascular disease, and hepatic disease are important entities.
   (*b*) Surgical:
   Previous operations, whether of a rectocolonic character, or in organs closely associated with this tract.
   (*c*) Venereal:
   Gonorrhea, lues.
   (*d*) Habits:
   1. Drugs:
      Use of physics, opium, or other drugs tending to produce constipation and diarrhea.
   2. Tobacco, coffee, tea.
   3. Bowels, frequency, type, and whether any change in bowel habitus.
   4. Urinary.
   5. Abnormal habits:
      Sodomy.
   (*e*) Menstrual:
   Regularity, whether painful or painless, type of bleeding, and if accompanied by any bowel phenomena.

3. Present history:
   (*a*) Duration of symptoms:
      Sudden onset, insidious onset, whether initial attack or recrudescence of a previous attack.
   (*b*) Pain:
      1. Location.
      2. Duration.
      3. Nature.
      4. Relationship to stool.
   (*c*) Change in function:
      1. Constipation.
      2. Diarrhea.
      3. Loss of control.
      4. Condition of sphincter.
   (*d*) Character of stool:
      Number, consistency, shape, odor, reaction and whether mixed with discharge, presence of undigested food particles.
   (*e*) Discharges:
      1. Blood, mucus, pus, amount, and what state.
      2. Parasites, foreign bodies.
   (*f*) Protrusions:
      1. Character.
      2. Replaceability.
      3. Whether or not accompanied by subjective or objective symptoms.
   (*g*) Reflex symptoms:
      Urinary and genital, referred pains in other parts.
   (*h*) Constitutional symptoms:
      1. Loss of weight.
      2. Cough.
      3. Nervous derangement.
      4. Fatigue.
      5. Gout, diabetes, and their symptoms.

4. Laboratory findings:

Whether any previous work in hematology, bacteriology, or roentgenology has been done.

General Physical Examination.—The tendency is for the specialist to interest himself intimately in only those symptoms and signs which pertain to his particular field and to lay little stress on the rest of the human being. General physical examination is very important not only for the proper interpretation of phenomena as they present themselves in the rectocolonic tract, but also from the standpoint of prognosis and treatment.

Observe a patient as he enters the consultation room. Is his gait normal or is there a hesitancy in walking? Painful conditions about the anus such as fissure, thrombotic piles, abscess, and fistula will oftentimes make the afflicted one cautious in his locomotion. When the individual attempts to sit down and does so guardedly usually preferring to sit on one buttock only and utilizing the edge of a chair it is safe to assume he has one of the above conditions or at least one should be suspected.

Loss of weight, falling in of the cheeks with hectic flush and pearly white conjunctivæ suggest tuberculosis. In such cases the lungs should be examined carefully and in doubtful cases resort made even to fluoroscopy and *x*-ray. A tuberculous lung will frequently elucidate the nature of a fistulous tract, an extensive pelvirectal abscess, or an unyielding diarrhea. Fixity and inequality of the pupils suggests central nervous system lues, and will explain a relaxed incontinent sphincter. Cachexia, particularly in an individual around forty, should put us on our guard for a possible malignancy. Anemia may be quite profound from the continued bleeding of prolapsing piles, and not infrequently the hemoglobin will fall to as low as 40 or 60 per cent. Chronic ulcerative colitis, polyps, benign, and malignant tumors, produce a degree of anemia, depending on the blood loss. Heart, if decompensated, will cause stasis in the portal circulation and be accompanied by large prolapsing hemorrhoids and considerable bleeding.

Examination of the abdomen should be made in the upright and recumbent positions. Diastasis recti with lax abdominal-

wall protuberance or pendulousness will suggest ptosis; if contour, uneven a possible mass and malignancy. In the recumbent posture feel for tenderness or mass in the appendicular, gall-bladder, cecal, splenic, and sigmoid regions. The entire length of the colon must be palpated. In the average individual the cecum and sigmoid are easily palpable. Thickening and tenderness of the former suggest chronic inflammation or tuberculosis; and tenderness of the latter, impaction, inflammation; and if signs are acute and similar to appendicitis—an acute diverticulitis. Masses, obstructions, or impactions can be mapped out in the thin subject.

The liver should be examined for enlargement, irregularity, and texture. A cirrhotic liver would be a contraindication for operating when severely bleeding piles co-exist. A nodular liver is usually due to syphilis or is secondary to carcinoma of the rectum or other parts of the gastro-intestinal tract. Circumscribed swelling in the gall-bladder region is often due to hydrops of the gall-bladder or if in liver region an amebic abscess. Enlarged spleen may cause fecal stasis, as can also a dropping of the kidneys.

In the protuberant abdomen always attempt to elicit a fluid wave, for ascites may be due to cirrhosis of the liver, decompensated heart and kidneys, generalized carcinomatosis, or rectal cancer with liver involvement.

Palpate the inguinal glands. Infections or malignancy in this area will produce enlargement of these lymph-glands, depending upon the nature of the process and the stage of the disease.

Examination of Anus, Rectum, and Colon.—*Inspection.*—It is surprising how much one can learn from inspection alone. It is best to put the patient in the left or right lateral prone position depending on the source of light, with the knees flexed to as near the abdomen as possible. Bright illumination must be available. Sunny daylight is best and in the absence of this, either a headlight of a focusing type or appropriate floor lamp will suffice. The perianal region is exposed by separating the buttocks, one hand on each side. Any malformation of the bony landmarks should be noted, particularly of the sacrum and coccyx.

The skin over this region should be noted for fistulous openings, especially, with ingrowing hairs, as these will be found to communicate with a pilonidal cyst. The perianal skin is frequently excoriated as result of discharges coming from within the bowel or from a fistulous tract with external opening. Loss of pigment in the perianal skin is characteristic of pruritus ani, and may also occur in kraurosis vulvæ with extension toward the anus. In pruritus the skin may be thickened and thrown into hypertrophied radiating folds, or be thin and dry, cracking and bleeding easily when stretched. Note the presence of previous operative scars. An improperly cut sphincter explains incontinence.

Indurations should be noted, and are usually due to abscess or fistula. Tuberculous fistulæ are not sensitive to the touch unless there is a secondary infection and the openings gape more. Sebaceous cysts, epithelioma, and chancre also develop at the anal margin, the latter usually occurring in the region of the posterior commissure. Loss of fat in the ischiorectal fossa is suspicious of malignancy or other wasting diseases, as tuberculosis, diabetes, etc.

With the buttocks separated, holding the finger-tips to as near the anal margin as possible, and instructing the patient to bear down, imitating a bowel movement, it is possible to note any protrusions and judge their relationship to the surrounding structures. External hemorrhoids occur in the form of skin-tabs. Thrombotic piles are located in the perianal region, are bluish in color, tender to the touch, fusiform in shape, and the long axis is directed toward the anal canal.

One must differentiate between condylomata and skin-tabs, prolapsed polyp and prolapsed internal piles, sentinel pile of fissure and epithelioma of anus.

Condylomata are wart-like excrescences, firm to the touch and have a nodular cauliflower aspect. They arise from the skin-edge by a distinctly defined base, are whitish in color, and distributed around the entire margin of the anus, usually in large numbers. If the Wassermann is negative, they may be due to irritating discharges coming in contact with the tender integument in this region.

When a polyp prolapses through the anal canal, it is found to be entirely covered with mucosa except its pedicle, and is easily replaceable.

Prolapsing hemorrhoids have a mucosal covering only on the upper part; when reduced they are found to come from above the mucocutaneous juncture.

True prolapse is red, reducible, covered by mucous membrane, slightly or not painful. There may be some bleeding and concentric rugæ are present.

Epithelioma is characterized by an excavated ulcer with coarse fungating granulations along its edges, has an area of induration around it, the inguinal glands are enlarged, and biopsy proves its nature.

Discharges: pus, mucus, blood, or combinations of the three, quantity, odor, and consistency are important. Their significance will be discussed later.

Eversion of the anal canal by exercising gentle traction on either side of the anal margin, at the same time asking the patient to bear down, will show internal hemorrhoids, hypertrophied papillæ, fissure, polyp, or internal thrombotic hemorrhoids, pin worms, or foreign bodies.

Palpation or Digital Examination.—Areas of tenderness in the perianal region or near the anal canal are significant. Circumscribed areas of tenderness with other evidences of inflammation are usually due to abscess, and their type depends upon location. If an external fistulous opening is present, there is usually a fibrous tract pointing toward the anal canal, and by following this, one can very frequently and readily locate the internal opening.

The texture of the skin should be noted. In pruritis, it is often thickened, hard, and parchment-like.

Digital examination is the most valuable single means of determining the nature of lesions of the last 5 inches of the bowel. It requires considerable experience before the finger-tip acquires the sensitiveness necessary to feel small papillæ, internal opening of fistula, polyps, cryptitis, etc.

Gentleness is very important in executing a digital examina-

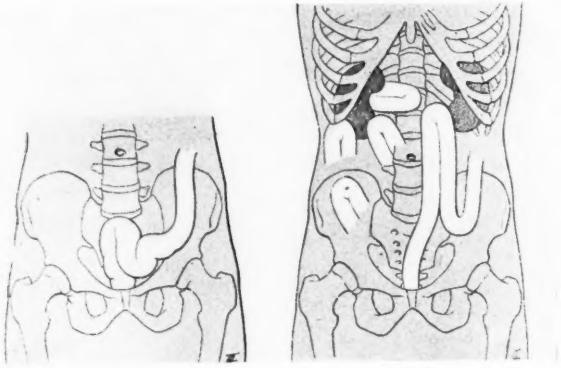
tion, and the way such an examination is performed will produce a lasting effect on the patient. The well-lubricated finger is gently pressed against the anal orifice. Soon the sphincter will relax and the finger begins its journey through the anal canal. One first notes the tone of the sphincter. Spasticity is usually due to some pathology within its grasp, the most common offender being a painful fissure, a blind internal fistula, or some ulceration very near the anal margin. Relaxation of the sphincter is generally due to spinal cord disease, old operation for fistula, or pederasty, the degree depending upon the extent of involvement. Loss of control of sphincter may also be due to encroachment of a neoplasm, repeated dilatation, prolapsing internal hemorrhoids, or prolapse of the rectum itself.

As the finger enters the anal canal, one can feel hypertrophied anal papillæ as small dentate projections, and frequently at their base enlarged crypts with tender, cryptic inflammation, these imparting to the finger the feel of a small indurated tract. Fissure and ulcerations are easily palpable, as is too the internal opening of fistulæ, usually located posteriorly in the anal canal between the two sphincters. As one proceeds, the finger goes into the ampulla. Note the state of the mucous membrane, whether dry or moist. Relaxation indicates atony. One can here feel polyps or whatever pathology is present. It is a good plan, while the finger is high in the rectum to have the patient bear down. Very frequently the bowel will impinge on the finger and feel like the cervix of the uterus. This is due to sigmoid prolapse, and is a frequently unrecognized condition. Sausage-like mass felt in the rectum of a child, accompanied by evidence of acute obstruction, with bloody mucous stools is pathognomonic of intussusception.

One gains an intimate idea of other pelvic organs by rectal examination; carcinoma of the prostate is first discovered by routine rectal examination. Seminal vesicles too can be mapped out as can the neck of the bladder. The cervix of the uterus, position of the uterus, and adnexal disease are amenable to interpretation by the examining digit.

When one considers that from an embryologic, neurogenic,

and vascular supply how intimately the pelvic organs are related, it is no wonder that pathology in the one will frequently give referred symptoms in the others. Pathologic changes producing vascular reactions have their remote effect on other organs in the pelvis besides the one affected. All of the pelvic organs are united in one grand nerve plexus, and an irritation arising from any source may be reflected as to appear to originate in another. Thus tumors of the ovary may cause rectal ulceration and even obstruction. Ovarian cysts, pelvic hematocele, hematoma, and inflammatory exudates into the board ligament usu-



A B

Fig. 156.—A, Most frequent type of rectrosigmoidiliac colon. B, Anomalies.

ally cause some degree of constipation. Advanced malignant growths of the uterus and its appendages invariably cause constipation and inflammation of the pelvic bowel. Carcinoma of the cervix and vagina invades the rectum and causes fistulous openings when in an advanced stage. Periproctitis may be caused by a congested or inflamed uterus and its adnexæ, crowding the bowel, adhesions fixing the rectum and sigmoid to other pelvic organs. Hemorrhoidal veins may bleed at the menstrual period simulating hemorrhoids, yet no actual hemorrhoids exist. Ulceration of the rectum and rectal conditions causing constipation may explain irregularity or even suppression of

menses. Congestion of uterus due to dysmenorrhea, a prolapsed ovary, uterine displacement or inflammation, may cause spasm of the anal sphincter.

On the other hand, fissure in ano, cryptitis, blind internal fistula, and inflamed hemorrhoids, may cause ovarian and uterine pain radiating down the posterior part of the sacrum and the thigh. Such disturbances are promptly cured when the rectal condition is successfully treated. Rectal pain and tenesmus may also be caused by inflammation of the bladder, while the operation for hemorrhoids is frequently followed by urinary retention. So, too, other inflammatory or productive changes frequently excite urogenital disturbances.

It is, indeed, fortunate that most conditions affecting the patency of the bowel are within reach of the examining finger. Thus, about 75 per cent. of strictures are in the lower 4 inches of the bowel. Malignant growths to the extent of about 85 per cent. are in the palpable portion of the rectum. Occasionally, impacted feces or foreign bodies affect the patency of the bowel, and their true nature is elicited by digitalization or instrumentation.

When a growth is present, it is important to determine its location, extent, movability or fixity, and whether low down or high up, hard or soft, and if it has invaded adjacent organs. These are important from the standpoint of type of operation to be performed and the probable tenure of life. It is significant also, whether or not the tumor impinges into the bowel lumen. More will be said of this in considering the subject from the standpoint of proctoscopy.

Digital examination is completed by grasping the coccyx between the examining finger in the rectum and the thumb outside to determine variations in contour, position, and mobility. Tissues just lateral to its tip should be compressed because in a certain number of cases of coccygodynia, the coccygeal plexus of nerves is tender.

Instrumental Examination.—Proctosigmoidoscopy.—Examination of the anal canal is accomplished with patient in the left lateral prone position or knee-chest. Pathology in this part is

readily exposed with a Kelly sphincteroscope or speculum of the Brinkerhoff type, utilizing either direct or indirect illumina-

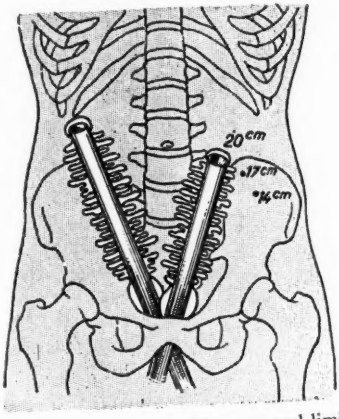


Fig. 157.—Different directions of sigmoidoscopy and limit of tube passing.

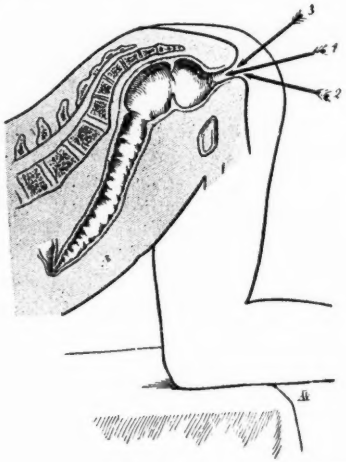


Fig. 158.—Positions in passing sigmoidoscope.

tion. The instrument should be well lubricated with a coarse variety of vaselin, and gently introduced, the direction being

downward and forward. One can easily note, when present, foreign bodies and worms, inflammatory conditions of the mucous membrane, simple or ulcerative hemorrhoids which prolapse into the tube on getting the patient to bear down, inflammatory swellings, abscess, cryptitis which permits a probe to be retrograded into it, new-growths, polyps, benign and malignant growths as well as traumatic lacerations, and fissure in an-

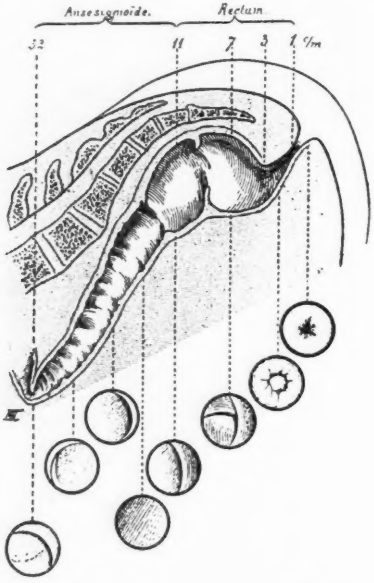


Fig. 159.—Sigmoidoscopic picture at different levels.

terior or posterior commissure. Higher examination of the rectum and sigmoid is best accomplished by an electrically illuminated, pneumatic proctoasigmoidoscope. The choice of such instrument requires considerable judgment. When one considers that the implement must enter a part which is usually not clean, covered with fecal matter and other discharges, it seems foolhardy to select one that has its illumination at the distal end. The light is quickly dimmed by this extraneous matter in the bowel lu-

men. So, too, the introduction of medicinal substances, usually of a pigmentary character, will affect the illumination, hence it seems logical that a type of instrument such as Yeoman's, equipped with a proximal light is the more useful one.

Proctosigmoidoscopy is easily performed even in children, at the office, the patient's home, or in the clinic, there being no need for anesthesia.

It is a good plan to examine the patient at first without any previous bowel preparation. One may then observe whether the rectum is empty or filled with stool; sigmoid, whether empty or fecal-laden; condition of stool, whether or not mixed with discharges. For a thorough and careful examination of the rectum and pelvic colon the patient should receive a dose of castor oil the night before and a 1-pint-plain-warm-water enema two hours before examination. The best position for proctosigmoidoscopy is knee-chest or knee-shoulder, and the patient's head should be made comfortable with appropriate pillows.

The tip of the instrument is gently applied to the anal orifice and the direction of pressure is downward and forward, until it passes through the anal canal, then upward and backward until it meets the obstruction of a pelvic brim. It is inadvisable to attempt to pass higher up without visualization, for there is always the possibility of damage to the tissues and certainly of causing the patient more discomfort than if the instrument is visually passed into the sigmoid flexure.

Proctoscopy reveals the condition of the mucous membrane, whether normal, atrophic, or hypertrophic. The normal mucosa has a salmon-like color, is smooth, and has sufficient moisture to make it glisten. Atrophic mucous membrane is dry, pale, the lustre is somewhat gone, and has little patches of dry fecal material stuck on here and there. Hypertrophic mucous membrane is thrown into concentric folds, has an abundance of secretion, and is somewhat reddened. Houstan's rectal valves are seen as one withdraws the scope or if one visualizes from the anal canal upward. If ulceration is present, its character can be intimately noted. If any productive changes exist in the bowel wall, their structure can be minutely examined. A common, unrecognized

condition is prolapse of the sigmoid, where the mucous membrane and even all coats insinuate themselves into the rectum.

Swellings, or other indurations, are easily discernible, as are, too, foreign bodies, worms, etc. In about 75 per cent. of the cases, the tube can be passed into the sigmoid flexure, the mechanical limit being the apex of the sigmoid which varies between 10 and 14 inches, depending upon the length of the mesentery, and the absence of angulation and fixation. If the tube does not pass easily, by gently distending the coil of intestine before the tube, it will follow along with comparative ease, unless actual obstruction exists. Very rarely, it is possible to see the ostium of a diverticulum through the sigmoidoscope and to pass a probe through it.

Phenomena Observed Through the Sigmoidoscope.—*Ulceration.*—Ulcerations may vary from superficial erosions to deep destructive lesions involving all the coats and even penetrating the bowel wall. Simple ulcers may occur from injury to the mucous membrane, by hard stools, or foreign bodies. The type of ulceration is dependent upon the infecting organism and whether or not secondary infection is present. They may be specific or non-specific, depending upon whether or not they are due to tuberculosis, syphilis, malignancy, actinomycosis, or amebiosis.

Tuberculous ulcers have a ragged, unhealthy, excoriated edge with a grayish base dotted with tubercles, smeared with a mucopurulent discharge and surrounded by inflamed edematous tissue. The ulcer edge, as a rule, is undermined and permits a probe for quite a distance. They are usually of a girdling type, occupying the breadth of the bowel, and vary in size from a small ulcer half the size of a pea to one almost involving half the breadth of the mucous membrane. These ulcers are usually multiple and occur in the rectum and sigmoid, as well as in the bowel higher up.

Hyperplastic tuberculosis is comparatively rare. It attacks the cecum and the rectum, and is often mistaken for malignancy. A differential diagnosis can only be made through the microscope. It takes years for tuberculous growth to develop whereas mal-

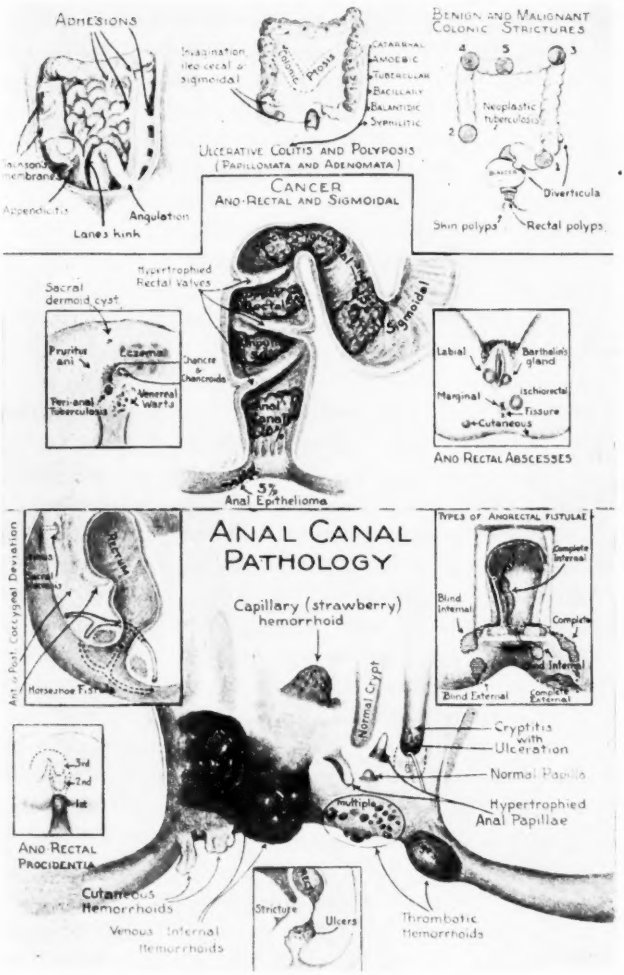


Fig. 160.—Anal canal pathology (Gant.)

ignant growths in a comparatively few months cause obstructive lesions of the bowel. This type of lesion is characterized by progressive, proliferating, hyperplastic proctitis, extending around

the bowel or forming an encapsulated, unilateral, firm, resisting, flat tumor. Neoplastic tuberculous outgrowths extend in either direction from the submucosa, enlarging the bowel externally and blocking it internally, and is often also confused with gumma and sarcoma. These neoplasms are attached to adjacent structures, are one or more inches in thickness, and are of a cartilaginous consistency. The gut proximal to the tumor is dilated, thinned, or ulcerated. Obstruction, rather than ulceration, typifies neoplastic rectal tuberculosis, hence the patient seeks relief from constipation, obstipation, alternating with loose movements, and finally diarrhea with persistent straining. Fibrosclerotic tuberculosis of the rectum and colon involves the bowel tunics and converts the gut into a rigid tube, the so-called gas-pipe colon; this being produced by a low grade infection in the submucosa.

The mucosa in amebic ulcers appears red and congested. The necrosed area is oval or irregular, and appears to project over the level of the mucosa. The shape varies and may be round or stellate. By careful examination small red papular spots may be seen dotted about the already well-defined ulcer, and may show white or yellow points of necrosis in the center.

Malignant ulcers occur singly and spread by direct contiguity, forming deep excavations with hard raised edges and showing a marked degree of infiltration at the ulcer base.

Syphilitic ulcerations are usually broken-down gummata, are apt to be multiple, are often accompanied by stricture or evidences of repair and are very common in negroes. Lues of the rectum causes plastic deposits in the bowel wall, causing thickness and lessening of the lumen. The walls are firm and inelastic, while the lumen is diminished.

Chronic ulcerative colitis presents an ulceration which may be superficial and punctate, and yet, on the other hand, so extensive as to involve all the coats. It is quite common to see the muscularis exposed in deep ulcers of this type. The more destructive ulcerations are due to secondary infection by pyogenic organisms.

Strictures of the Rectum.—About 75 per cent. of these occur in the lower 4 inches of the bowel and are usually due to hyper-

plastic changes following injury to the bowel wall by trauma, deep ulceration, or faulty repair in operation. Aside from these causes, syphilis is the greatest contributing factor. Strictures may be anular or fusiform, and in degree may vary from simple narrow, to total, occlusion of the bowel lumen.

Tumors of the Rectum.—The commonest non-malignant tumors are the adenomata or polyps. They occur singly or are multiple, and when multiple frequently involve the entire colon. Adenomata are usually pedunculated, the pedicle being short or long. The shorter and broader the pedicle, the more liable they are to malignant degeneration, particularly in the multiple variety. Pedunculated growths of any type presenting a short, broad base are always suspicious of malignancy.

Fibroma and adenofibroma—small, firm growths attached to the bowel wall—are occasionally met, in the rectum, and have little significance.

Dermoid and other cysts are infrequently encountered and most often in the posterior wall of the ampulla and lower rectum.

Of all forms of cancer in the body, $4\frac{1}{2}$ per cent. in females and $7\frac{1}{2}$ per cent. in males are cancers of the rectum. Of this percentage, 5 per cent. is in the anal margin, 10 per cent. in the anal canal, 50 per cent. in the ampulla, 20 per cent. in the upper rectum, and 15 per cent. in the rectosigmoidal juncture and sigmoid flexure.

There are two types of malignant tumor in the rectum—carcinoma and sarcoma. The former usually occurs in one of four types: (1) Medullary, soft, or encephaloid, (2) scirrhous; (3) colloid; (4) melanotic. The medullary form is pale in color and resembles brain substance, is very malignant, rapidly growing, and often assumes enormous proportions. This type forms metastasis early and recurs after extirpation. It is of a spongy consistency, and when cut or squeezed exudes a juice, so-called cancer milk, composed of degenerated cell nests. It is commoner than the scirrhous form and younger patients suffer with it. It also shows a decided tendency to invade neighboring organs.

Scirrhous carcinomas are hard and fibrous, occurring in the upper rectum. They are not as malignant as the medullary type because of a preponderance of connective tissue and few epi-

thelial cells. They are bluish-white in color and cartilaginous to the touch, undergo softening, and take on features of the medullary type.

Colloid cancers may be large or small, are usually soft, may remain stationary or grow quickly, show a very slight tendency to ulcerate or involve neighboring or remote lymph-nodes, and are not as common as the other types. Jelly-like material escapes from the colloid cancer, varying from a tablespoonful to a pint in twenty-four hours.

Melanotic tumors are rare in man, and are hard to distinguish from pigmented sarcoma. They are blackish in color, soft, vascular, and very malignant. They bleed easily, degenerate early, ulcerate and emit a dark, offensive discharge.

Sarcoma is rarer than carcinoma and varies in type as to tissue from which it originates. Thus we have fibro-, myxo-, glio-, melano-, chondro-sarcomata, depending upon the cells from which they originate. They are hard growths, involve a good deal of the bowel wall, and are sometimes difficult to differentiate from syphilitic stricture and hyperplastic tuberculosis of the rectum.

Consideration of Principal Symptoms.—The principal symptoms complained of are pain, bleeding, protrusion, constipation, diarrhea, itching, and various discharges. Associated with these are reflex pains referred to the other pelvic organs, headache, backache, pains down the thigh, indigestion, flatulence, and abdominal cramps.

Pain.—This is one of the most important symptoms and one which causes the sufferer to seek prompt relief. Its type and location vary depending upon the causative factor. When it occurs immediately after and up to two hours following a bowel evacuation, it is usually due to fissure in ano, or some pathologic condition within the grasp of the sphincter as blind internal fistula or an ulceration. A throbbing constant pain is almost pathognomonic of a suppurative condition, probably abscess. This pain is more intense before and during defecation with slight relief after the completion of the act, due to lessening of the pressure of the fecal mass. Sudden onset of pain following straining with stool or after lifting some heavy weight, accom-

panied by a small mass near the anal margin is indicative of a thrombotic pile. Pain here is aching in character and is due to distention of the part of edema. Tenesmus usually occurs in conditions in the rectum and pelvic colon and points to inflammation, tumor, stricture, neurosis, or it may be reflex from ureter, uterus, and adnexa. It is usually accompanied by a bearing down sensation and a desire to go to stool.

Change in Function.—A sudden change in a patient's bowel habitus, particularly when this function has always been regular, should warrant very careful investigation for it is frequently one of the first symptoms of malignancy or stricture.

Hypertrophy of the external sphincter with spasm will produce constipation, as will tumors from within and without pressing on the rectum as fibroids, ovarian growths, gravid uterus, and adhesions. Certainly every case of constipation, particularly in an individual past thirty-five, should warrant proctosigmoidoscopic and if necessary *x*-ray examination.

Persistent diarrhea should always be investigated for it is usually the expression of a localized irritation or disease. Morning diarrhea is a very early symptom of malignancy. The stool here has an unusually obnoxious odor and is characteristic.

The various inflammatory conditions in the upper rectum and colon are usually accompanied by frequency of bowel evacuation, and the higher the process the more frequent the attempt on the part of the bowel to empty itself. The character of the stool will depend upon the etiologic factor, so that it may be fluid, semifluid, mixed with blood, pus, or mucus, or may consist of mucus and blood alone.

Discharge of pus from the anus is usually due to fistula, ulceration, abscess, stricture, or malignant disease. Mucoid discharge is usually indicative of internal hemorrhoids, polyps, proctitis, beginning stage of malignant growth, or mucous colitis. Anal condylomata very frequently are accompanied by a copious and very offensive thin mucous discharge. Eczematous and pruritic conditions around the anus also are accompanied by a sour, offensive discharge.

Bleeding, next to pain, is one of the commonest reasons for

the patient's seeking advice. It is most often produced by internal hemorrhoids, and in this condition nearly always follows a bowel evacuation. It may also occur from fistula, ulcer, benign and malignant tumors, and the quantity of blood lost will depend upon the size of the vessel involved. One of the most alarming cases of hemorrhage from the rectum was seen by me in a patient who had been injected with phenol for the treatment of internal hemorrhoids, producing an extensive slough with the opening up of a comparatively large-size vessel. Fluid blood is indicative that the source is near the rectum and anus. If the blood is clotted or organized, naturally it must come from conditions higher in the gastro-intestinal tract, or to have remained *in situ* for considerable time. Any case of bleeding from the rectum, anus, and colon should be given the advantage of all the diagnostic methods available in order to rule out any important pathology.

Itching may be caused by local eczema, pruritis, parasites, herpes, and local irritations caused by hemorrhoids, ulceration, cryptitis, foreign bodies, coloproctitis, neoplasms, irritating discharges from vagina, and healing wounds—all these may be etiologic factors in causing this most distressing symptom. So, too, there may be constitutional causative factors such as errors in diet, excessive imbibing of strongly alcoholic drinks, rheumatism, diabetes, and gout. Reflexly, itching around the anus may be the result of ureteral stricture, ureteral calculus, prostatitis, phimosis, bladder calculus, gall-stones, and uterine disease.

***x*-Ray Examination.**—It is always wise to do all instrumental examinations before the patient receives barium for *x*-ray examination, otherwise some very intimate conditions may be obscured by this agent. For the lower 8 to 10 inches of the bowel, sigmoidoscope certainly gives more information than any other agent at our command. Above this, *x*-ray is an important addition to our diagnostic armamentarium. Complicated fistulous tracts, and particularly those which have been operated on before should be inspected with either bismuth paste or one of the lipoid preparations of iodin and *x*-rayed by the stereo-

scopic method prior to operation. There is some objection to the use of bismuth paste in that its consistency interferes with draining in those fistulas which have extensive inflammation and profuse discharge. Lipiodol seems to be a better agent for this purpose, and the results are as good.

Fluoroscopy after a barium enema is of prime value because it visualizes all segments of the colon, detects adhesions, and demonstrates obstructions, flexures, angulations, and any other factor that might impede its flow. Fluoroscopy and *x*-ray after a barium meal are important to determine points of intestinal obstruction of a chronic character, motility of the colon, outline of the appendix, competency of the ileocecal valve, kinks, or stasis. By pressing on the various colonic segments while the barium enema is going in, one can note the presence or absence of adhesions binding down that particular part of the bowel. The colon should also be examined fluoroscopically after the barium enema is expelled. Naturally, the part is a bit distorted by the fluid, and when it has passed out a truer concept of structural proportions may be gained.

In cases of chronic constipation, the *x*-ray furnishes us with a definite means of ascertaining where the fecal matter is. The average person has at least one bowel movement in twenty-four hours, generally in the morning following breakfast. On the other hand there are thousands of instances on record of individuals who have not had evacuations for two to forty days, without any comparative ill-effect. Normally, food reaches the cecum within four hours of the time it enters the stomach, the hepatic flexure in six hours, the splenic flexure in nine hours, the iliac colon in eleven hours, and the pelvic colon in twelve hours. Here it is retained until expelled by tonic contractions of O'Beirne's sphincter at the pelvorectal juncture. After giving barium in oatmeal porridge, one can determine just how long it takes for this to reach the various portions of the colon, and if there is any delay just where it is located.

In neoplastic and obstructive conditions—above the realm of visualization by instruments—the *x*-ray is an invaluable aid. In chronic ulcerative colitis it will show absence of haustrations,

tubular appearance of the colon, and flocculent changes in the continuity of the surface of the barium on the bowel wall.

In fecal stasis *x*-ray shows the location plainly.

Biopsy.—Tissue examination is a positive means of diagnosis and should be utilized where the character of the process is of any prognostic importance and of operative significance. The type of operation would naturally be different if a tumor is malignant or non-malignant, as will the method of procedure vary if a fistulous tract is tuberculous or non-tuberculous. All suspicious tissue should be examined microscopically. In malignant disease there has been some controversy as to whether or not the removal of a part of the tumor mass for histologic examination could possibly cause any difference in a dissemination of the growth. If one exercises a certain degree of caution in the method of biopsy, one can totally disregard any deleterious effects arising from the small tissue trauma involved. One should remove tissue from a tumor mass in several places, preferably at the summit and base of the growth for very frequently a hyperplastic change will be malignant at the base and non-malignant at the apex or summit, and vice versa. The Yeoman biopsy forceps is a very fine instrument for this purpose and is sufficiently long to work through a sigmoidoscope, and has an excellent cutting edge, removing ample tissue for examination purposes. When using this instrument, it is advisable to thoroughly carbolize the tissue attacked or touch it up with the actual cautery after the operation. Lately I have been advocating the use of electrocautery snare using an electrical cutting current for this purpose. It has the advantage of causing no bleeding, sealing the lymphatics immediately, and rendering a greater amount of tissue available for examination.

Laboratory.—Laboratory examination is a valuable adjuvant to rectocolonic diagnosis and should be taken advantage of more frequently. Complete blood examinations are important in the profound anemias resulting from chronic bleeding, from hemorrhoids and other sources, and are an aid to the seriousness of a suppurative condition if accompanied by fever.

Wassermann examination of blood-serum should be done in every case of tumor, ulceration, stricture, or suspicious fistula.

Bacteriologic examination of the stool, discharge, and ulcer scrapings is important from a standpoint of treatment and prognosis. Bargen and Buie of the Rochester Clinic have come out quite recently with the claim that they have isolated a specific micro-organism as a causative factor of chronic ulcerative colitis, and have recommended treatment with vaccine filtrates. They claim some remarkable cures. The attempts at obtaining this specific organism by other investigators, using the same technic and media, have not been of signal success. So, too, the use of the vaccine filtrate sent to us from the Mayo Clinic in some of our severe cases has met with far from encouraging results. Autogenous vaccine made from discharges in the bowel and ulcer bases, or sometimes pus from an apical tooth abscess made into a vaccine and injected, have resulted in some remarkable cures. Whether this result is due to the foreign protein effect or the antibactericidal action of the vaccine is a question. All discharges should have smears made, and the nature of the infecting organism determined.

Urine examination should be a routine measure in all cases of pruritis and intestinal stasis. Quite frequently an unsuspected glycosuria will be found that will explain the tormenting itch, or a uric acid diathesis that has the same effect.

Microscopic examination of a stool for ova or various parasites is important as well as bowel function tests to seek for undigested food particles, etc.

Summary.—The early utilization of diagnostic methods in diseases of the rectum and colon is very important and is indicated in all cases when there is any question of bowel dysfunction. Every case of constipation, particularly if it is a deviation of a person's normal habit, should be thoroughly gone over. Any bleeding from the tract should be investigated. Any abnormal discharge, vague symptoms anywhere in the body, such as fatigue, dizziness, pains and aches all over the body especially rheumatism, and asthma, when there is no ap-

parent cause, will sometimes be cleared up by removing a fecal stasis existing in the rectum, sigmoid, or colon.

Proctosigmoidoscopy should be utilized more frequently where there is pathology in any of the pelvic organs for it is surprising how sometimes a simple rectal operation will remove distressing symptoms in the adjacent structures. Quite frequently, the absence of rectal pathology in spite of definite subjective symptoms on the part of the patient will direct one's attention to the fact that the phenomena are probably referred, and a stone in the ureter, a fibroid uterus, a cystic ovary, or pelvic hematocele will be discovered which might otherwise have been overlooked. All diarrheal states that persist should never go without tubular examination of the bowel.

In closing, let me again emphasize that the early utilization of these definite diagnostic methods is imperative. To be of value they should not be delayed and put off from week to week, for sometimes a short interval of time will determine the operability or non-operability of a malignant growth, and make a great difference in the outlook as to life. So, too, comparatively simple anorectal conditions when recognized early are quite easily amenable to surgical procedures that do not keep the afflicted individual away from his work for any length of time, whereas if these conditions remain untreated subsequent measures will necessarily be more drastic, cause greater inconvenience, and require a longer lying-in period.

CLINIC OF DRS. S. BILOON, M. M. HARRIS, AND A. I. RINGER

FROM THE MEDICAL DIVISION OF THE MONTEFIORE HOSPITAL

INFECTION AND DIABETES

INFECTION plays a very significant rôle in the natural history of diabetes. It may precipitate the disease, it commonly aggravates the disease, and it often, through the intermediation of sepsis and coma, terminates it.

It has been repeatedly observed that during the course of an acute infectious disease with fever, there is a hyperglycemia and a transient diminution in the carbohydrate tolerance.[1, 2, 3] Recently it has been shown that glucose injected into the bloodstream of infants ill with infection, is not removed from the bloodstream as rapidly as is glucose injected into normal infants.[4] It has been shown further that the function of the liver, as estimated by a study of levulose tolerance, was below normal in children sick with acute infections.[5] Geyelin[6] has reported the histories of 8 patients who were non-diabetic before the onset of an acute infectious disease, and who became true diabetics during the course of the acute infection. Stengel[7] has also reported the clinical course of 5 patients, whose antecedent health was known and diabetes definitely ruled out, and who during the course of an acute infection became true diabetics; 4 of these patients having had ketosis. Apparently during the course of an acute infection it is possible to develop hyperglycemia, disturbances in liver function, inability to utilize injected glucose, and a full-blown diabetes.

The experience is general today that in established diabetes infection lowers tolerance, aggravates the symptoms, and frequently induces a severe acidosis. This is seen very clearly in

patients receiving insulin. With the onset of an acute infection, increasing doses of insulin are necessary to make possible the burning of adequate amounts of sugar and to control the acidosis. It is, however, true, that certain types of infections are more prone to reduce the tolerance of diabetics than others. Infections of the respiratory tract and the gastro-intestinal infections are notoriously liable to precipitate severe acidosis. Representative cases from our service will illustrate this:

J. H., 9132R, age twenty-two years, a moderately severe diabetic under insulin treatment, developed an acute laryngitis and within twenty-four hours was brought into the hospital unconscious. CO_2 in plasma 12 volumes per cent. Blood-sugar 370 mg., exhibiting all the clinical signs of diabetic coma.

J. L., 11649R, age fourteen years, a severe diabetic developed an upper respiratory tract infection with temperature. Remained at home under treatment with insulin but without any change in the dosage to meet the emergency. Entered hospital after five days in severe acidosis bordering on coma. Much larger doses of insulin were necessary to bring him under control.

A. T., age five years. Very severe diabetic who developed an acute otitis media while under control in the hospital. She went promptly into severe acidosis. Blood-sugar 430 mg., with all the clinical evidences of impending diabetic coma. During the convalescence from this infection an acute exacerbation of her otitis occurred. She went promptly into severe acidosis bordering on coma again. In each instance much larger doses of insulin were necessary to control the acidosis than were necessary before the onset of the otitis media.

It will also be seen from our series of cases that low-grade chronic infections, while they may diminish tolerance, usually do not produce the sharp change in the clinical picture of a case of diabetes that follows upon the onset of an acute infection.

Infection through the intermediation of sepsis and coma, may terminate the disease. This is a fact thoroughly attested by the experience of clinicians everywhere. The occurrence of coma uncomplicated by infection is comparatively rare. Coma supervening upon infection is very common (Peters,[8] Campbell,[9] Joslin,[10] Williams[11]).

We are reporting 20 cases of diabetes in whom infection occurred as a complication. These cases are representative of the

material seen in our service and will serve to illustrate the principles which underlie the management of this complication. It is always our plan in the treatment of infection in a diabetic to control the infection rapidly by the necessary measures. If operative interference is required, we recommend it immediately unless the general condition of the patient is such as to make hazardous the operative risk necessary to control the infection. Under these conditions we attempt to treat the acidosis first and operate at a time when the patient is a better operative risk. The disturbed metabolism in the cells of a diabetic patient makes it imperative that only the necessary surgery be done and that, very gently. At the same time we insure the burning of a sufficient amount of carbohydrate to render normal the burning of protein and fat, and in this way control acidosis, using insulin if it is required to attain this end. By these means we attack the infection, which is the cause of the increasing severity of the diabetes, and re-establish in the body-cells a metabolic state approaching normal. If we can accomplish this, the presence of hyperglycemia and glucosuria is comparatively unimportant at this time.

We have adhered strictly to this practice for a number of years without having had cause to regret it. We make no effort to keep the blood-sugar at a normal level in a diabetic who is ill with an acute infection. We do, however, regard it as absolutely necessary to provide at least 100 gm. of carbohydrate a day and to insure its combustion by insulin. If the ketosis is marked we give still greater quantities of carbohydrate. In our judgment it is fundamentally wrong to give too little carbohydrate and fundamentally right to give enough to control ketosis despite a high blood-sugar. We have seen wounds heal by primary union in the presence of continuous hyperglycemia and even in the presence of a moderate ketosis.

The importance of this procedure to our minds cannot be overestimated since, until very recently, it has been almost the general teaching that it was necessary to keep the blood-sugar normal in a diabetic, even at the cost of marked undernutrition; and since the introduction of insulin, at the cost of repeated

hypoglycemic reactions. Certainly in patients ill with acute infection this is not only unnecessary but undesirable and unsafe.

Included in our series are the following types of infection:

		Cases.			Cases.
(1)	Pneumonia	1	(15–17)	Osteomyelitis	3
(2–6)	Acute appendicitis	5	(18)	Cholecystitis	1
(7–8)	Mastoiditis	2	(19)	Perinephritic abscess	1
(9–10)	Carbuncle of neck	2	(20)	Salpingitis	1
(11–14)	Abscess of soft parts	4			

Discussion.—It will be seen from the tabulated chart that 15 out of the 20 cases of diabetes reported show a marked change in the clinical picture of the disease immediately following the onset of the infection. Thirteen of these cases were mild before the onset of the infection. Two cases were moderately severe, and were the only ones which showed ketosis before the onset of the infection. All 15, however, became very sick with high blood-sugar, marked ketosis, and in 3 instances, cases Nos. 10, 13, 19, coma supervened. Of the 5 cases which showed no change in the clinical course subsequent to the onset of the infection, 3 were cases of chronic osteomyelitis, 1 acute appendicitis, and 1 case of mastoiditis. Case No. 5 survived an acute infection of the mastoid with operation without change in the severity of diabetes, and died in another hospital six months later of peritonitis which followed an acute attack of gangrenous appendicitis during which the diabetes became very severe.

Four of the acute infections which required operative intervention had glucosuria during the postoperative period, and 1 case also had ketosis. Three of these were laparotomies, 1 an operation for abscess of soft parts. Three wounds healed by first intention (cases 2, 3, and 18). Case 11 healed slowly due to necessity for drainage.

All but 3 of the cases reported, received insulin during the period of the acute infection. Only 1 case was severe enough to receive insulin before the onset of the acute infection. Of the 16 cases which survived the infection, all returned to a mild state after the infection subsided. One of the cases deserves special mention in this connection.

No.	Age.	Duration of diabetes.	Nature of infection.	Duration of infection.	Severity of diabetes before infection.	Severity of diabetes during infection.	Treatment of infection.	Result.	Remarks.
1	24	9 years.	Lobar pneumonia (Pyelitis postpartum).	14 days.	Mild.	Moderately severe ketosis. Blood-sugar 190 mg. CO_2 41.2 vols per cent. Pyelitis—blood-sugar up to 180 mg.	Rest. General supportive dietary drug treatment of pneumonia and pyelitis.	Cured of both infections Delivered of normal baby at term.	Temperature during pneumonia not above 99.5° F. Temperature during pyelitis not above 100° F. After recovery blood-sugar between 90 and 100 mg. on a fasting stomach.
2	58	4 years.	Chronic appendicitis. Acute appendicitis.	1 year. 2 days.	Mild—no ketosis.	Blood-sugar 320 mg. before operation. Blood-sugar 364 mg. postoperative. Ketosis marked. Blood-sugar on the 19th day postoperative 159 mg.	Appendicectomy under gas and oxygen anesthesia.	Cured.	Heavy glucosuria for 1 week after operation. Wound healed by first intention. No complications.
3	9	4 months.	Acute appendicitis.	3 days.	Mild—no ketosis.	Mild—glucosuria moderate, no ketosis.	Appendicectomy under ether.	Cured.	Moderate glucosuria during entire postoperative period. Wound healed by first intention. No complications.
4	30		Acute appendicitis.	1 day.	Mild—no ketosis, blood-sugar 105 mg.	Mild.	Appendicectomy.	Recovery.	
5	52		Acute appendicitis. Peritonitis.	2 days.	Severe persistent glucosuria and ketosis on maintenance diet.	Very severe ketosis.	Appendicectomy with drainage.	Cured.	Following operation there was a marked decrease in the severity of the diabetes. During 8 years postoperative, diabetes has remained mild.
6		1 year later.	Appendicitis with peritonitis.		Mild.	Very severe during appendicitis, blood-sugar 330 mg.	Laparotomy, appendicectomy with drainage.	Died.	Cause of death, peritonitis.
7	45	6 months.	Mastoiditis.	1 week.	Mild—blood-sugar up to 154 mg.	Mild during mastoid infection.	Mastoidectomy.	Recovery.	No complications. Comparative mildness of diabetes during the mastoid infection. Marked increase in severity with the appendicitis.
8	51	11 years.	Mastoiditis.	3 months.	Mild with very few exacerbations.	Severe—ketosis blood-sugar 195 mg.	Mastoidectomy under gas and oxygen anesthesia.	Cured.	Blood-sugar after operation 142 mg. No glucosuria during convalescence. Insulin given.
9	47	5 years.	Carbuncle of the neck.	3 weeks.	Very mild—no symptoms of any kind.	Very severe blood-sugar 480 mg. CO_2 28 vols. per cent.	Complete excision. Dietary control and insulin.	Cured.	Two months after onset of infection, insulin stopped. Blood-sugar 150 to 180 mg. No ketosis, no glucosuria on liberal diet.

No.	Age.	Duration of diabetes.	Nature of infection.	Duration of infection.	Severity of diabetes before infection.	Severity of diabetes during infection.	Treatment of infection.	Result.	Remarks.
10	53	19 years.	Carbuncle of the neck.	2 weeks.	Mild.	Very severe. Blood-sugar 327 mg. Coma, heavy glucosuria. Loss of 40 pounds in two weeks.	Incision and drainage.	Died.	No insulin available at that time.
11	46	10 years.	Abscess of the knee.	2 weeks.	Mild.	Severe. Blood-sugar 419 mg. Heavy glucosuria. Marked ketosis.	Incision and drainage under local anesthesia.	Cured.	Blood-sugar before discharge 320 mg. Wound healed slowly. Glucosuria present throughout healing period. Insulin given.
12	47	7 years.	Ischiorectal abscess.	3 weeks.	Mild—very few symptoms.	Severe—loss of weight 45 pounds in 3 weeks. Blood-sugar 418 mg., before drainage. After drainage 117 mg. One year later 155 mg.	Incision and drainage under gas and oxygen.	Healed.	Mild diabetes, severe during infection. Always aglucosuric on 75; 75; 200. Returned to mild state after treatment
13	53	10 years.	Abscess of the plantar surface of the foot.	3 weeks.	Mild.	Very severe. Blood-sugar 553 mg. Urea nitrogen 28.6 mg. CO_2 12.8 vols. per cent. Coma.	Incision and drainage with Dakin's technic.	Died.	Patient entered hospital in coma. Active insulin treatment and operation not effective. Died in coma.
14	53	18 years.	Abscess of the thigh.	4 weeks.	Very mild.	Severe—temperature 105°F. with chills. Heavy glucosuria. Blood-sugar 230 mg. Ketosis.	Incision and drainage under gas and oxygen.	Cured.	Patient sugar-free during convalescence with the help of insulin.
15	60	12 years.	Osteomyelitis and cellulitis of the foot.	6 months.	Mild with an occasional increase in severity.	Mild—sugar-free on diet of 50 grams of carbohydrate 75 of protein and 150 of fat. Blood-sugar 176 mg. No ketosis.	Incision and drainage.	Wound healed.	Mild diabetes in old man. Infection low-grade. Diabetes controlled with insulin.
16	45	18 years.	Chronic osteomyelitis of second and third metatarsal bones of right foot. Abscess of plantar surface.	3 months.	Mild.	Moderately severe. Blood-sugar 270 mg. No ketosis.	Conservative. Wet dressings. Incision of superficial abscess. Rest in bed.	Healed.	Mild diabetes. Infection low-grade. Controlled with diet and insulin. Bones of foot healed slowly.
17	66	5 years.	Chronic osteomyelitis abscess of the left foot.	5 weeks.	Mild—very few symptoms.	Mild. Blood-sugar 153 mg. No glucosuria nor ketosis.	Incision and drainage under gas and oxygen. Carrell-Dakin technic.	Improved. Healing not complete on discharge.	Mild diabetes. Infection low-grade. Controlled with diet and very small doses of insulin.

17	69	5 years.	Chronic osteomyelitis abscess of the left foot.	5 weeks.	Mild—very few symptoms.	Mild. Blood-sugar 153 mg. No glucosuria nor ketosis.	Incision and drainage under gas and oxygen. Carrell-Dakin technic.	Improved. Healing not complete on discharge.	Mild diabetes. Infection low-grade. Controlled with diet and very small doses of insulin.
18	52	10 years.	Cholecystitis with cholelithiasis.	10 years.	Mild with occasional attacks of increased severity.	Severe—blood-sugar 312 mg. Glucosuria and ketosis despite dietary control and large doses of insulin—72 units daily. Diet 50 grams of carbohydrate, 75 of protein and 150 of fat. Glucosuria 24 grams daily average.	Cholecystectomy under gas and oxygen with small amount of ether.	Improved. Wound healed by first intention.	Glucosuria during period of healing with some ketosis. After operation on a diet of 50 grams of carbohydrate, and 75 grams of protein, and 150 of fat and insulin, 15 units, three times a day, patient excreted 5 grams of sugar in the urine.
19	55	8 years.	Suppurative pyelonephritis. Perinephritic abscess. Antecedent abscess of toe.	4 weeks.	Moderately severe. Slight ketosis. Was receiving insulin before onset of infection.	Very severe. Heavy glucosuria. Blood-sugar 382 mg. Coma before laparotomy.	Incision and drainage of perinephritic abscess under gas and oxygen.	Died.	Cause of death infection and diabetic coma.
20	44	3 years.	Chronic salpingitis with acute exacerbation.	3 years.	Mild.	Severe. Blood-sugar 279 mg. Heavy glucosuria and ketosis. Temperature 100° to 102° F. during period of acute exacerbation.	Rest and supportive treatment.	Improved.	With subsidence of infection general condition improved and diabetes became much milder.

Case No. 5 was under observation for a period of two years before the onset of the attack of acute appendicitis in 1918. This patient was a severe diabetic with glucosuria and ketosis even while under treatment. It was necessary to place this patient on a fast day or green vegetable day in order to clear up his urine. On a maintenance diet he soon developed glucosuria and ketosis again. Subsequent to the operation, the removal of an acute gangrenous appendix, his diabetes became very mild and has remained mild for a period of eight years. At present he is sugar-free and has no ketosis on a diet of 100 grams of carbohydrate, 75 grams of protein, and unlimited amounts of fat. His sugar tolerance, studied in April, 1917 after ingestion of 25 grams of rye bread, was as follows:

Fasting blood—110
Forty-five minutes after—180
Ninety minutes after—164

Operation May, 1918.

Glucose tolerance test in October, 1918, after 80 grams of bread:

Fasting blood—100
Forty-five minutes after—130
Ninety minutes after—135

Certainly the removal of his appendix was followed by a remarkable change in the clinical course of his diabetes. He was under rigid dietary supervision before his acute infection, but no appreciable improvement in his diabetes could be measured until his postoperative period. Then the change began and has persisted throughout eight years of continued observation.

Management of a Diabetic Patient During the Course of an Infection.—Infection is the principal cause of coma in a diabetic. The central metabolic problem therefore in the management of a diabetic patient during the course of an acute infection is the control of acidosis and the prevention of coma. The treatment must, however, be directed at the same time against the infection since it is the direct cause of the acidosis.

At the outset certain elementary matters must be arranged. The patient must receive the general supportive treatment which is primary during the course of any acute infection. Specific treatment against the infection, if available, should be given immediately. Competent nursing attention is imperative in order to insure the proper regulation of diet and administration of insulin. In the absence of a competent nurse the physician should examine each voided specimen of urine himself for sugar and diacetic acid and give the insulin himself. There are too many sources of error to delegate these duties to a member of the family in the event that the patient is not in the hospital. It is our growing conviction that no compromise on this matter is permissible. Whenever the attention to detail is for any reason relaxed the results of treatment are unsatisfactory.

Let us assume for example that a moderately severe diabetic is confined to his home, ill with an acute infection of the respiratory tract with temperature, heavy glucosuria and ketosis. The general nursing care and medical treatment have already been secured, and the prevention of acidosis and coma concerns the doctor alone for the present. The solution stated very simply is this, the patient must burn 60 to 100 gm. of carbohydrate in twenty-four hours and must receive about 5 to 10 gm. of sodium bicarbonate daily while the ketosis persists. Fluids in sufficient quantity to prevent dehydration have to be supplied.

Called to such a patient, with the problem presented, the first procedure consists in the giving of a dose of insulin subcutaneously (20 to 40 units). Fluids in the form of milk, orange juice, broth, and coffee are to be given at two hourly intervals, 6 ounces at each feeding. Should vomiting occur proctoclysis of 5 per cent. glucose and 1 per cent. sodium bicarbonate solution must be promptly instituted, 500 c.c. every six hours. This done the blood should be examined for CO_2 combining power if a laboratory is available. But treatment must never wait upon the blood examination unless there is a real diagnostic problem. If the clinical condition of the patient becomes alarming as evidenced by increasing drowsiness and hyperpnea, another dose of insulin should be given. It is well to provide about

25 gm. of glucose in some form to cover each dose of insulin except the first. There is usually a marked hyperglycemia in impending acidosis, and even if the first dose is 40 units there is not much danger of too great a lowering of the blood-sugar. In some clinics it is the practice to give insulin and glucose intravenously in cases bordering on acidosis or coma. We use the intravenous or subcutaneous route for glucose only as a last resort. It is never the method of choice.

It is our practice to give small amounts of alkali by mouth or by Murphy drip to all patients with acidosis. In this we are in agreement with other clinics.[13, 14, 15, 16] Joslin, however, has not been giving alkali for many years, and due to the weight of his opinion the routine use of alkali is perhaps less general than its importance warrants. The deviation in normal metabolism, which is seen in any case of progressive acidosis in which the body excretes increasing amounts of ammonia and less of urea, points the way to the rational use of alkali. That in acidosis the alkali reserve of the body is depleted through combination with and excretion of newly formed abnormal acids is evidenced by the lowering of the CO_2 combining power of the blood, and is undisputed. Certainly then, on strictly physiologic grounds, there seems to be an indication for alkali in diabetic acidosis. The doses originally recommended, 6 to 8 gm. six times daily, were certainly too large and often made the patient very ill, and must occasionally have produced an alkalosis. Those patients with acidosis and coma due to the retention of organic acids other than the ketonic acids and those diabetic patients in whom the acidosis is the result not only of abnormal fat and protein burning but also of retention of acid metabolites due to a complicating nephritis certainly require alkali. One cannot combat these conditions with insulin and glucose alone and, occasionally, as described by Campbell, nothing will raise the CO_2 combining power of the blood except alkali.

There seems to us, therefore, to be no valid reason why alkali should not be routine in the treatment of diabetic coma. No harm can come from its use, since this use is based upon sound physiologic doctrine. No good can come from with-

holding it. It is true that often it is possible to control diabetic acidosis with glucose and insulin and without alkali. Joslin has given ample evidence of this. But this is not sufficient grounds for broadcasting the teaching that alkali must always be avoided in diabetic coma.

The amount to be given need not exceed 10 gm. in twenty-four hours (1 gm. alkali according to Woodyatt will raise the CO_2 combining power of the blood 1 volume per cent. in a man weighing about 85 pounds). Thus with a low CO_2 to start with, no harm can possibly come from a rise of 10 volumes per cent. And even when given on top of a normal CO_2 combining power (45 to 50 vol. per cent.) no alkalosis can possibly intervene with this dose.

With the subsidence of the toxemia and drop in temperature without the development of acidosis it is safe to allow a soft and easily digestible diet containing milk, cereal, toast, eggs, and clear broth. Never curtail carbohydrates while the patient is still sick with the acute infection. It is only necessary to make carbohydrate burn in sufficient amounts to render normal the burning of fat and protein. This can usually be done by the use of insulin. It is always wrong to give large quantities of vegetables to diabetic patients ill with fever. It is not safe to attempt to control glucosuria and hyperglycemia by dietary regulation until the acute illness has passed. During the period of severe illness, however, it is well to have a constant moderate glucosuria in each voided or catheterized specimen. In this way chances for hypoglycemic reactions are reduced to a minimum.

Since the examination of the urine for glucose and diacetic acid is to be used as a therapeutic guide, it is sometimes essential to know whether the patient has a true nephritis or kidney insufficiency due to dehydration complicating his diabetes. Either of these complications may decrease or render absent the ketone bodies in the urine,[17] and the doctor may decide against the coma as being diabetic. This must be a rare occurrence since in an active service we have never seen a case during the last eleven years. However, it does occur, and whenever the patient is drowsy and has hyperpnea without a diacetic acid reaction in

the urine, it is well to remember that one may be dealing with a complicating nephritis. Examination of the blood for glucose, CO_2 combining power, and urea will clear up the difficulty. If an examination of the blood is not obtainable, it is good practice to give insulin and glucose as long as the hyperpnea and drowsiness persist; and glucose should be given in quantities sufficient to maintain a steady glucosuria to avoid hypoglycemic reactions.

Once the infection is under control the danger from acidosis is decreased, and with hyperpnea and drowsiness no longer present, supervision of the patient may be somewhat relaxed. A balanced diet can then be arranged to contain vegetables and sufficient protein to insure nitrogen equilibrium. All the urine should be saved in twenty-four-hour specimens, and enough insulin given in divided doses to control the glucosuria. It is safe to allow 1 unit of insulin for every 2 gm. of sugar in the twenty-four-hour specimen of urine.

There is no incident in the life of a diabetic which has more tragic implications than the onset of an acute infection. There are few situations in medical practice where intelligent care on the part of the physician can be productive of so much benefit to the patient.

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CLINIC OF DR. BRET RATNER

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ALLERGY IN CHILDREN

I WOULD like to present to you* this morning a group of allergic cases, and I shall try to demonstrate the various types of conditions we encounter in this particular phase of pediatrics.

We have been enabled to study these cases more carefully than in the past through the establishment of the "Crane Research Fund for the Study of Allergic Diseases in Children," for children are admitted into the hospital so that they may be studied most intensively.

One of the essentials in the study of these cases is a proper analysis of the history, and I should like to stop a few moments to discuss this matter of history taking before proceeding with the presentation of the cases. It has been thought that allergy is an hereditary condition, but we believe there is not enough evidence to make us limit ourselves to this point of view. Several years ago, I reported a group of cases suffering from allergy due to rabbit hair,[1] and expressed the opinion, then, that these cases were acquired. Since that time additional evidence has been presented in the literature in favor of the acquisition of allergy, and we are keeping careful family records.

We inquire most carefully into every manifestation of the disease, its inception, the time it occurs (whether during the day or night, after a meal, summer or winter), whether it is related to sleep, its relationship to certain places and substances such as contact with animals.

We elicit a minute description of a typical attack, trying to determine whether or not the condition is explosive in nature or

* Fourth year medical students.

insidious in development; whether it occurs with vomiting, or is accompanied by profusely running eyes, or sneezing. We inquire further into the very early histories of these children in an attempt to determine whether the child, when taking a certain food for the first time, has had any reaction, or any marked dislikes for certain foods, whether he has had infantile eczema or urticarial attacks, and is now coming to us with asthma. This particular group of questions requires very intimate knowledge of the entire problem, and as we question we may gain an inkling of the possible type of condition or substance that may be the cause of this particular patient's asthma, eczema, or urticaria. I might make certain observations here which will clarify the situation. For example, if a child gives a definite history of having vomited egg for the first time, becoming nauseated every time he eats egg, or some egg-containing food, we believe the condition may be closely related to the taking of egg. On the other hand, should he get his attacks exclusively at night, and if there is no history of eczema or any food dislikes, we lean toward the supposition that possibly he is getting his attacks from some feather or rabbit hair pillow, etc.

However, if he gives a history of attacks at any time during the day, or at any time during the night, throughout the year, we feel inclined to believe the child is in the category of multiple sensitizations, and that possibly he reacts to both food and epidermals (feathers or animal hair). There are, also, very remarkable cases of children developing their asthmatic attacks when they go to a particular place, such as on a visit to a grandmother, suffering the attacks immediately after these visits. There are histories of attacks occurring only in the summer, or only upon a farm, in which the indications are very obvious.

Our next phase of history taking pertains to a particular mechanism described by us recently in the Journal of Immunology[2] and the American Journal of Diseases of Children.[3] This particular aspect of history taking may frequently solve the entire problem. We are very particular to inquire into the antepartum history of the mother, and question very carefully into her diet during this period. We have found

that many mothers for some reason or other develop inordinate cravings for a particular food. She may, for example, indulge excessively in wheat-containing foods, or eggs, or milk, and so on, and it seems that these mothers, eating excessively of this particular type of food, are unable to metabolize the excessive amount of proteins ingested, These proteins thus find their way into the circulatory system in an undigested state and cause a contact with the fetus which may so sensitize it that after birth, when this child partakes of the particular food which the mother indulged in excessively, he develops a profound allergic phenomenon, such as vomiting, urticaria, or perhaps eczema or asthma.

It is obvious that if this mechanism be true, a large group of the so-called exudative diatheses in infants would be prevented from developing if all mothers were taught not to indulge their cravings during the antepartum period, and we hope to carry on this work so that these cases may be prevented from occurring.

Three to four hundred skin tests are done on each child by the ordinary scratch method which is painless and which the child does not mind at all. A careful analysis of the urine is made each day. The blood chemistry is studied thoroughly from many standpoints. The general status of the blood is determined, including eosinophil counts, etc. *x*-Rays of the sinuses and chest are taken. Intracutaneous von Pirquet, Schick, and Dick tests are made. The results of all these investigations are very carefully analyzed, and, by coupling them with the history, we attempt to determine, if possible, the exact cause of the child's asthma, eczema, urticaria, or hay-fever. There are a certain number of cases with an etiologic cause that we cannot determine. Nevertheless, in these cases, we continue our studies in the hope of some day unearthing the particular offending substance.

In those cases where we are fortunate enough to find the cause, we have, next, the problem of eliminating that particular substance from the child's environment, thus helping him to overcome his sensitization.

Following these brief, prefatory remarks, I would like to present to you various cases studied in the manner outlined, and so give you a more specific idea of the results obtained.

ANTEPARTUM CASES

The first group of cases are the result of excessive indulgence in certain foods by the mother during her antepartum period.

Several weeks ago, a mother came to the clinic with an infant who had been suffering from eczema for a month and a half. Up to six months of age, the child had been breast-fed. Her skin was perfectly normal and it was only after she began to eat cereals, such as farina and cream of wheat, that eczema started to develop. Upon inquiry into the antepartum history, I learned the mother had had an inordinate craving for wheat foods, and had consumed large amounts of bread, cakes, crackers, etc. As she put it, she seemed to be eating either cake or bread throughout the day. After the child was born she suddenly discontinued her inordinate consumption of wheats. As soon as this antepartum history was obtained, I requested my assistant to test the child against the various wheat proteins, and a positive reaction to wheat gliadin, wheat globulin, and wheat proteose was obtained. This child was taken off wheat cereals immediately, and, in order to give her her full quota of starchy foods, we substituted rice, corn, and oat cereals for wheat. A mild salve was applied to the face to allay itching and to heal the already damaged skin. Within a short period of time, the eczema cleared up and the skin returned to its normal state. It might be of interest here to state that treatment of infantile eczema in the past was fraught with bad results because salves, *x*-ray treatments, etc., merely helped to heal the skin, but, if the child continued to eat the particular offending food, no amount of salve would help. Even though the skin had been cleared, the condition returned. In certain instances, however, under such treatment it clears gradually because of the mechanism of spontaneous desensitization.

Another interesting case was a boy five years of age who had had asthma for a year. Careful investigation of his history indicated that his attacks were referable to the ingestion of foods, seeming to bear a particular relationship to candies and desserts. It was a striking fact that, upon inquiry into the antepartum history of his mother we learned that throughout her antepartum period she had had a craving for nuts. When we tested the boy for nuts, he gave positive skin reactions to several of the common nuts. When nuts were eliminated from his diet, there was a complete clearing of his asthmatic attacks, whereas if he relaxed his watchfulness and indulged in nuts the attacks recurred. An analysis of this history brings out several points that may be helpful: the relationship of the boy's asthmatic attacks to meals, and the fact that he developed his asthma at the age of four, about the time when he first began to eat nuts. The case indicates, also, an unusual development of asthma without a previous occurrence of eczema.

Another case, equally interesting, was a child who, when given hard-boiled egg at ten months of age, tolerated it with complete immunity, but when given coddled egg one month later, developed a generalized urticarial eruption upon first ingestion. She was tested and found to be sensitive to egg white. The mother gave a very frank history of having indulged excessively in eggs and egg foods during antepartum. I saw this girl, first, seven years ago. By giving her carefully diluted amounts of egg-white, we have apparently succeeded in desensitizing her so that she is now able to take normal amounts of egg. She has had no other allergic manifestations for the past seven years.

One of the most striking cases I have encountered was a child who suffered from an extremely severe form of eczema, involving practically the entire body. Upon inquiring into the history, I ascertained that the mother because of a nauseous pregnancy, could tolerate only eggs, consuming as many as seven or eight a day. This child, like the one last reported, was shown to be sensitive to egg white, and during the course of observation while inadvertently taking egg, manifested his first asthmatic attack.

I might cite many more instances of this nature to bring out the importance of the influence of antepartum diet, but I wish merely to indicate today that, in most of these cases I have studied, practically all types of allergic manifestation were traceable to a contact with the particular food which the mother had craved and indulged in excessively during the antepartum period. It behooves those physicians, therefore, who have pregnant mothers in their charge to stress particularly the importance of not indulging cravings and, if there is an inordinate hunger, to emphasize the necessity of taking a large variety of foods in small quantities, rather than indulging in one particular kind.

MULTIPLE SENSITIZATIONS

One of the most complicated forms of allergy is presented in those cases where the child reacts to a multiplicity of substances, and I would like to say here that it is only after every one of these substances is known, can you obtain good results.

A case in point is a boy who reacted to various meats. Elimination o these from his diet, however, did not clear up his asthmatic attacks, or the persistent, moderate eczema of his face which was very interestingly aggravated by his father, who had a large mustache and who, being a butcher, often stroked it with hands that had touched meat. Whenever he kissed the boy, a reaction that was urticarial in nature and gradually became eczematous, developed on the boy's face. To return to the asthmatic symptoms,

however, we traced these attacks to the inhalation of cat-hair dust. The boy's aunt was a cat fancier, and whenever he visited her home he was permitted to play with her cats. Almost invariably on these visits he developed an attack of asthma. In this instance, we had a case of multiple sensitizations, where the elimination of a certain food removed only one cause for the condition, and elimination of cat hair removed the other.

Another child gave a reaction to fish, but, upon inquiry into his history we learned that the boy knew of this sensitivity and that his mother kept fish out of his diet. We did a complete series of tests and found that he was sensitive to wheat, chicken, horse dander, pyrethrum, and glue. The horse dander sensitization may have accounted for several attacks that occurred while he stopped on a farm. Certain attacks were discovered to be due to wheat sensitization. The mother stated that a number of years before she was compelled to use a great deal of roach powder, to which we attributed his sensitization to pyrethrum, a substance used largely in insecticides. Furthermore, the boy was warned not to lick postage stamps or envelopes because of his sensitization to glue, which is a fish product. So, you see, in these instances one must realize the importance of knowing a child's sensitivity to various substances, all of which may be causative factors of one or another of his attacks. Then only will good results in this work be brought about.

In order to demonstrate certain points of importance regarding multiple sensitizations in urticaria, I will relate the story of a case I had the privilege of observing for a period of years, rather than present other cases that have not been studied for a long period of time. This was a boy who developed a most intense form of urticaria. It kept him awake at nights with a most intractable itching. At times his penis swelled so that the urinary passage was blocked, and occasionally both of his eyes were swollen completely shut. We found him to be sensitive to eggs, wheat, milk, chicken, peas, and fish, and it seemed, at the time, that it would be almost impossible to help him. Nevertheless, with the intelligent co-operation of his mother, we were able to do so. We told her, first, to discontinue all wheat that had not been thoroughly cooked—that is to permit him to eat only toasted bread, zwieback, etc.—and to replace wheat by some other form of starch, whenever possible. Next, we directed attention to the milk situation, and the boy drank only milk that had been cooked for fifteen or twenty minutes. All eggs were eliminated from his diet with the exception of eggs boiled for thirty minutes. Fish and peas were kept out entirely. Chicken was allowed in small, thoroughly cooked portions. The boy was thin, extremely anemic, and worn out. He has been observed over a period of four years, and it is remarkable that on this regimen, thoroughly carried out, he has thrived exceedingly well and has developed into a normal child.

Certain incidents in this boy's history will bear recital. One day the mother, while eating salmon, touched her fork with her fingers and got salmon on them. Undressing the boy after this meal, she found to her surprise that wherever her fingers touched him an urticarial eruption ensued. She told me, also, that the patient's little brother, who had been eating codfish, kissed him one day on the left cheek near the eye, with the result that both his eyelids promptly presented an angioneurotic edema.

I would like to indicate here that, by eliminating certain foods, by heating, and by providing substitutes we are enabled to treat these patients most intelligently, and by gradually allowing them minute amounts of the foods to which they are sensitive, an immunity against them may be developed.

DUST SENSITIVE CASES

A certain group of workers have intimated that many asthma cases are sensitive to house dust. This, to my mind, is a non-specific manner of studying these asthma cases, and does not help us solve the problem of a particular asthma. As I have indicated in a previous clinic,[4] it is not dust *in toto* that interests us, but the specific animal or vegetable substances that finds its way into the dust. To illustrate, the boy who developed his asthmatic attack when coming in contact with a cat gave a very definite reaction to the dust of his aunt's house; but gave a negative reaction to the dust of his home. I would like to present the following case as an example of the importance of testing, not against dust, but adhering strictly to the specific substances in the environment.

This boy was studied by another worker and was found sensitive to dust. His asthma was not alleviated, and he was sent to our department where he was studied most carefully. We tested him against all of the proteins and found that he was definitely sensitive to goose feathers as well as to canary feathers, against which he had not been tested before. We learned, too, that in his household a great many feather comfortables were in use, and that a large amount of feather dust was present in the rooms. Furthermore, a canary had been in the family's possession for about five years, coinciding with the period during which the boy's asthma had been in evidence. So, in this instance, we were not interested in dust in general, but, specificially, in eliminating feathers and the canary from the boy's environment.

Another point in this boy's asthmatic history was the fact that he was sensitive to nutmeg and cloves. The mother told us she was very fond of using these spices in the preparation of her food, and it is of interest that during the boy's severest attacks she fed him beef broth plentifully seasoned with nutmeg.

SINGLE SENSITIZATION

In this last group of cases, we have obtained our most brilliant results. Where an individual—as I pointed out a number of years ago—is sensitive to rabbit hair, the elimination of the offending pillow will result in a complete cessation of asthmatic

attacks. The boy I present to you today is a typical example of reaction to rabbit hair, for by investigating his mattress, pillows, etc., we found his mattress stuffed with rabbit hair. Elimination of this rabbit hair from his environment will result in a complete cure, providing he continues to remain away from the substance. So, we have innumerable examples of children sensitive to a single substance such as egg, milk, feathers, the eradication of which from the food, or from the environment brings about a brilliant result.

I would like to close these comments with a plea, and this suggestion to you who are about to enter the practice of medicine, to regard allergic phenomena in a child in the broad manner indicated today, and to realize that these conditions—no matter how slight—should be studied most carefully in order to put yourselves in a position to advise the mother properly as to the management of the child's life and, above all, assist in the work of preventive medicine in this, as in other fields.

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CLINIC OF DR. HERMAN ELWYN

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THE PRINCIPLES OF TREATMENT IN ACUTE NEPHRITIS

WITH our present-day conceptions of the diseases of the kidneys, we include under the term "nephritis" a number of distinct clinical entities. The diseases included under the term "acute nephritis" have this in common, that the glomeruli of both kidneys are primarily affected, and that they are characterized clinically by the presence of blood in the urine, either macroscopically or microscopically, in addition to albumin. They differ, however, in other features. The diseases are: embolic focal glomerulonephritis; non-embolic focal glomerulonephritis; and acute diffuse glomerulonephritis. These diseases are not only clinically but also pathologically distinct entities. We shall briefly characterize their essential features.

Embolic Focal Glomerulonephritis.—This disease has a definite etiology. It occurs only in the course of subacute bacterial endocarditis, almost always due to the Streptococcus viridans, in the bacterial stage. Although both kidneys are affected, only a limited number of glomeruli are involved, the number varying with the individual case. The involved glomeruli are rarely entirely affected, and in the greater number of cases, one or more capillary loops only are diseased. The glomerular changes are the result of the lodging of minute emboli in the capillary loops. These emboli consist of clumps of streptococci derived from the diseased valves. These cocci have slight chemotactic power, and therefore do not produce suppuration or any marked leukocytic infiltration. The process in the glomerulus is a minute infarct which involves the obstructed capillary loops, with destruction of their cells, followed by organization and heal-

ing with scar formation. In the cells of the tubules the changes are insignificant, and the blood which is found in the lumen can be traced to the diseased glomeruli. The above changes have been found in dogs following the experimental production of bacterial endocarditis with the S. viridans.

Clinically the disease is characterized by the presence of blood in the urine either macroscopically or microscopically in addition to albumin and casts. It occurs only in the course of subacute bacterial endocarditis. Since only a portion of the glomerulus is involved and only a limited number of glomeruli, the rest is free to carry on the function of the kidney. There is, therefore, no appreciable loss of kidney function, no renal insufficiency, no increase in the non-protein nitrogenous waste substances in the blood, and no uremia. There is no increase in blood-pressure. Convulsions do not occur.

Non-embolic Focal Glomerulonephritis.—This disease which we shall call briefly focal nephritis is of frequent occurrence. It occurs in the course of acute infections of the upper respiratory tract especially in streptococcus infections of the tonsils or pharynx. It occurs occasionally in the course of other infections, and together with acute interstitial nephritis in the first week of scarlet fever. In the course of the latter disease it is important to differentiate the focal nephritis from the acute diffuse glomerulonephritis, which never occurs in the first week of the disease, but always about eighteen to twenty-one days after the onset. I have also seen repeated attacks of focal nephritis following the recovery from acute diffuse nephritis.

The disease is not frequently seen at autopsy because of its benign character. The changes found are irregularly distributed. Not all the glomeruli are involved, and either the whole glomerulus or only a few loops are affected. In the affected loop the capillary walls are thickened and granular or form small areas of coagulation necrosis. Other loops are dilated forming small lacunæ filled with blood. Some of the loops have ruptured into the capsular space which is filled with blood. In other loops there are found thrombi or leukocytic infiltration. The capsular epithelium is swollen and in some places proliferated. In the

proximal convoluted tubules of the affected glomeruli desquamation of the epithelium may be observed, and blood is frequently found in addition to the albumin.

In this form of nephritis also the main clinical symptom is the hematuria. In addition there are found in the urine moderate amounts of albumin, and in the sediment, red blood-corpuscles, leukocytes, and hyaline and granular casts. At the beginning there may be a slight reduction in the amount of urine and a slight increase in the non-protein nitrogen of the blood, but this is not frequent and lasts only a few days. Kidney function is normal as only individual glomeruli and individual loops in a focal distribution are affected, and the rest is able to carry on the function of the kidney. Edema never occurs as part of this disease and there is no increase in blood-pressure and no uremia. Organisms, especially the streptococcus, have been obtained from the urine.

The disease is of a benign character and in many cases the hematuria disappears within two weeks. In other cases, however, the hematuria persists for months or years in a mild degree and becomes marked with the onset of an acute infection of the tonsils, pharynx, or accessory sinuses of the nose.

Acute Diffuse Glomerulonephritis.—In this disease all the glomeruli with the exception of a very small number are involved. The degree of involvement is more or less uniform. The whole glomerulus is swollen and fills the capsular space more fully. The capillary loops are swollen, dilated, and filled with a protoplasmic network in which are imbedded numerous cellular elements among which leukocytes and endothelial nuclei can be distinguished. Red blood-corpuscles are completely absent. The capsular epithelium shows slight proliferation and desquamation of cells and in places the glomerulus is adherent to the capsule. The cells of the proximal convoluted tubules show swelling, fatty and hyaline degeneration, and desquamation of cells. The interstitial tissue is edematous and there are areas of cellular infiltration.

All these changes disappear entirely on recovery. The formation of crescentic masses of proliferated epithelium in the

capsular space, and the hyalinization of the glomeruli, which are probably irreparable changes, are not part of the features of acute diffuse glomerulonephritis, but of the subacute and subchronic forms of the same disease.

In the etiology of acute diffuse glomerulonephritis are concerned: the infectious diseases, streptococcus infections, and exposure to cold and wet. Of the infectious diseases, scarlet fever is of chief importance, and the disease occurs eighteen to twenty-one days after the onset. The discovery of the streptococcus as the causative agent of scarlet fever is added evidence that this organism is perhaps the main etiologic factor in acute diffuse nephritis. In streptococcus infections of the throat and tonsils, acute diffuse glomerulonephritis occurs about seven to fourteen days after the onset. Subacute bacterial endocarditis due to the Streptococcus viridans is frequently complicated by acute diffuse nephritis in addition to the embolic focal nephritis which is characteristic of the disease.

Clinically this disease differs totally from the focal nephritides. In addition to the hematuria, albuminuria, and the presence of casts, there is diminution in the amount of urine even to complete anuria. With the onset of the disease there is an increase in blood-pressure which is moderate at first and is absent only in the very mild cases. There is also edema, either general or localized to some region in the body. The hematuria, the edema, and the increase in blood-pressure are the main objective phenomena of this disease. In addition, evidence of renal insufficiency is found in the increase of the total non-protein nitrogen, and of the urea, uric acid, and creatinin in the blood. There are great variations in individual symptoms, and in the severe cases, those with marked diminution in the output of urine and those with anuria, the symptoms of true uremia appear. Convulsions, the so-called acute convulsive uremia, are a frequent complication.

Acute diffuse glomerulonephritis is a curable disease and the larger number of cases recover completely. When the disease lasts longer than six to eight weeks, the probability is strong that it has passed into a subacute or chronic form. Whether the pa-

tient recovers from the disease or not depends a good deal upon the treatment.

Treatment.—Before treatment is undertaken it is necessary that a correct diagnosis should be made. This is not difficult. In the case of the embolic glomerulonephritis, the fact that it occurs only in the course of subacute bacterial endocarditis separates it at once from the other forms. The treatment of this disease is that of the endocarditis.

The other two forms, the non-embolic focal and the acute diffuse glomerulonephritis, may be confused when the latter is of a mild degree, and no edema or increase in blood-pressure has been observed. When edema is present even to a slight degree or a definite increase in blood-pressure has been observed, the presence of an acute diffuse glomerulonephritis must be diagnosed. Frequently, however, a focal nephritis occurs following the subsidence of the acute diffuse form. The following case is an example:

F. B., male, aged thirty, has had in childhood measles, diphtheria, and scarlet fever. There was no history of kidney diseases following the scarlet fever. Seventeen days before the present admission the patient had an attack of tonsillitis followed by a peritonsillar abscess which was incised. Two weeks later he noticed swelling of the feet, legs, and genitals, puffiness of the face, and diminution in the amount of urine. On admission, there was edema of the face, genitals, legs, feet, and over the sacral region. The urine had a specific gravity of 1.018, and contained large amounts of albumin, numerous red blood-corpuscles, and hyaline and granular casts. His blood-pressure was 160 systolic and 100 diastolic. The blood chemistry was: total non-protein nitrogen, 60 mg. per 100 c.c.; urea nitrogen, 44; uric acid, 3.6; creatinin, 2; *i. e.*, a moderate amount of nitrogen retention. Under appropriate treatment. the symptoms subsided. Eight days after admission the blood-pressure was 126 systolic and 84 diastolic, the edema had completely disappeared, and the blood chemistry was as follows: total non-protein nitrogen, 31 mg. per 100 c.c.; urea nitrogen, 16; uric acid, 2.9; and creatinin, 2. The urine contained a heavy trace of albumin and a few casts, but no red blood-corpuscles.

So far the case was one of acute diffuse glomerulonephritis of moderate severity from which the patient was recovering. On the eleventh day after admission the patient complained of a sore throat and the temperature was found to be 101° F. The pharynx was red and the tonsils red and swollen. At the same time the urine was found to contain blood grossly and microscopically. There was no increase in blood-pressure, no edema, and no changes in the blood chemistry. The tonsillitis and pharyngitis subsided in three

days, and the blood in the urine was reduced to a few red blood-corpuscles. A week later there was a recurrence of the acute tonsillitis and with it the reappearance of blood in the urine. Again there was no increase in blood-pressure, no edema, and no changes in the blood chemistry. There was no recurrence after the subsidence of the second attack.

In this case the recovery from acute diffuse glomerulonephritis was followed by an attack of focal nephritis which recurred once.

Treatment of the Non-embolic Focal Nephritis.—Treatment in the acute case must be directed primarily toward the disease of which the focal nephritis forms a complication. With recovery from the original disease the focal nephritis usually disappears promptly. Rest in bed as long as there is blood in the urine is necessary in the case of an acute infection. No special diet except what the original disease calls for is necessary.

If the focal nephritis recurs repeatedly or persists for a long time, any focus of infection in the body should be sought for and removed. The tonsils form one of the chief sources of infection, and even slight evidence of any disease in them should be at once followed by their removal. Often with no obvious evidence of disease in the tonsils pockets of pus are found on their removal. Removal of the tonsils is often followed immediately by an increase in the amount of blood in the urine. This does not last long when the tonsils have actually been the source of infection, and complete recovery frequently results. Other foci of infection, such as in the teeth or accessory sinuses, must also be completely eradicated. Drugs which are used to stop the bleeding from the kidneys have no effect whatever.

Treatment of Acute Diffuse Glomerulonephritis.—In the treatment of this disease a good many antiquated notions are still prevalent. One still sees repeatedly the administration of large quantities of fluid in this disease at a time when the kidneys are unable to eliminate them, in an effort to remove some hypothetical poison from the body. It is necessary that we have certain principles to guide us in the treatment of this disease based on an understanding of what actually happens in the kidneys. We must realize that we have no means to influence directly the pathologic process in the glomeruli. We know, however, when the kidneys are given sufficient rest and time,

the pathologic process subsides and the glomeruli again resume their function. We also know that when the body is at rest, the metabolic activities are at a minimum, and the end-products of protein metabolism which the kidneys must eliminate is therefore reduced to a minimum. We have then as the first principle of treatment:

1. *Complete Rest of the Patient Throughout the Course of the Disease.*—As a consequence of the hindrance to the flow of blood through the glomeruli there is an accumulation of fluid in the body and an accumulation of the end-products of protein metabolism. In an attempt on the part of the organism to maintain the normal blood volume, the excess of fluid is accumulated in the tissue spaces as edema. This also helps to distribute the nitrogenous waste products, and their concentration in the cells of the tissues, where they act as poisons, is lessened. Here we have another hint as to treatment and we may formulate two additional principles:

2. *The limitation of the intake of fluid as long as there is a hindrance to the flow of blood through the glomeruli.*

3. *The limitation of the intake of those food substances which have as their end-products of metabolism nitrogenous substances, that is, the limitation of the intake of protein.*—The increase in blood-pressure which accompanies the onset of acute diffuse glomerulonephritis helps to force a stream of plasma through the obstructed capillary loops of the glomeruli. At the same time this increase in blood-pressure increases the work of the heart in a sudden manner. This results in a demand on the reserve power of the heart, which may be inadequate because of the lack of time allowed for the heart to hypertrophy. The work of the heart is increased still more by the fluid which is retained in the vascular system when there is little or no tendency to edema formation; or, when in spite of the edema all the excess of the retained fluid has not been removed from the vascular system. We have then as a further principle in treatment:

4. *The lessening as much as possible of the work of the heart and the prevention and treatment of cardiac failure.*—The increase in blood-pressure is moderate in degree. It may, how-

ever, at any time take a sudden rise. It is then followed by cerebral symptoms, of which headache is the first and is prodromal of more serious phenomena; namely, vomiting, sudden blindness, convulsions, transient paralyses, which are classified together under the term "acute convulsive uremia." The appearance of a sudden increase in blood-pressure, of headache, or of any other prodromal symptom, is therefore an indication for another principle in treatment:

5. *The Prevention and Treatment of Acute Convulsive Uremia.*—In the severe cases the onset of the disease is sometimes followed by anuria. This means that the obstruction to the flow of blood through the glomeruli is of such a degree that even with the increase in blood-pressure (when present) blood-plasma cannot be forced into them. If the anuria is not relieved, poisoning by the retained waste substances must necessarily follow as soon as these substances have reached a certain concentration in the blood and tissues. We have therefore:

6. *The Treatment of Anuria.*—When we approach the treatment of acute diffuse glomerulonephritis with these principles in mind, the greater number of cases do not present serious difficulties.

Rest.—Complete rest in bed is indicated throughout the duration of the disease, that is, until the blood chemistry and the blood-pressure have returned to normal and until the hematuria and the marked albuminuria have disappeared. Frequently a trace of albumin remains long after all the other symptoms have disappeared.

Limitation of Fluid and Food.—This in addition to rest is our chief means of treatment. For the first few days the limitation should be extreme, even to complete starvation, as advocated by Volhard. The effect of Volhard's cure "by hunger and thirst" is in some cases magical. The blood-pressure falls, diuresis sets in, the edema disappears, and the blood chemistry returns to normal. The starvation cure is, however, difficult to carry out in many cases. Fluids should be limited to as low a figure as possible. Most patients will not suffer when the fluid intake is limited to 500 c.c. in twenty-four hours for three days.

As the patient improves, the fluid intake is increased to 800 c.c., to 1000 c.c. and more.

It is easier to withhold food completely for two days. When this is possible it should be done. If food is given in the first two days, it should be low in protein, and the amount should be as little as possible. The food should consist of white bread, salt-free crackers, rolls, sugar, rice, sweet fruits, fruit juices, cream, butter, and vegetables. With the disappearance of the symptoms a more liberal diet is allowed. The avoidance of sodium chlorid lessens thirst and helps to control the food intake.

The maximal diminution of food and fluid intake, preferably with a previous two days of fasting, is soon followed by increased diuresis, decrease of the hypertension, and disappearance of the edema. It thus helps in diminishing the work of the heart and in preventing convulsive seizures.

The Prevention and Treatment of Convulsive Seizures.—The convulsions are usually preceded by an intense headache. When the blood-pressure is taken at that time, it will be found to be increased. The means of preventing the convulsions are those which will quickly reduce the sudden increase in blood-pressure. For this we may use drugs, venesection, and lumbar puncture.

The most important of the sedative drugs is chloral hydrate. With the appearance of the headache, this should be given in doses of 0.5 to 1 gm. dissolved in water and well diluted every three to four hours. This drug causes a lowering of blood-pressure even in small doses. With the onset of the convulsive attack chloral hydrate in doses of 2 gm. in 5 per cent. solution should be given by rectum and repeated as required. The administration of chloroform for the control of convulsions must be resorted to if necessary. Instead of chloral, morphin sulphate may be used hypodermically in doses of 0.016 gm. Catharsis should be induced by a saline.

For the further prevention of convulsions, venesection may be employed with the removal of about 300 c.c. of blood. When convulsions have set in, lumbar puncture will frequently stop further repetition.

All these means so far mentioned help to diminish the work of

the heart and to prevent cardiac failure. However, any presence of cardiac embarrassment such as increase in pulse-rate and cyanosis is an indication for the use of digitalis. Tincture of digitalis in doses of 2 c.c. every four hours may be used until the cardiac symptoms are relieved, and it is seldom indicated for longer than three days in succession.

The Treatment of the Edema.—The proper limitation of the food intake alone is sufficient to increase the diuresis and diminish the edema. Drugs are useless in the first few days. When the edema persists after the blood-pressure and the blood chemistry have returned to normal, drugs of the xanthin group may be used in small doses and for short periods. Of these theobromin sodium salicylate, 0.3 to 0.5 gm., and theocin, 0.2 to 0.3 gm., are the best. Of some help in the treatment of edema is the use of warm baths. They help to mobilize the edema fluid and do not weaken the patient as much as the hot pack.

The following case is an example of acute diffuse glomerulonephritis, treated in accordance with the above mentioned principles.

B. H., male, white, thirty-three years of age. February 24, 1926, patient was taken ill with a sore throat, slight fever, headache, and general malaise. He was in bed for two days when his fever disappeared and he recovered completely. March 3d, he noticed that his face was swollen as well as his arms and legs. At the same time he noticed a diminution in the amount of urine. His status on admission, two days later, was that of a well-developed and well-nourished white male, with moderate edema of the face and trunk, and marked edema of the legs and genitals. There was no fever. The pupils reacted to light and accommodation. The teeth were well cared for, the tongue was coated, the tonsils large but not inflamed. The lungs were negative. The apex-beat was felt in the fifth interspace 8 cm. from the mid-sternal line. The aortic second sound was accentuated. There were no murmurs. The rate was 96, with normal sinus rhythm. The liver was felt two fingerbreadths below the costal margin; the spleen was not palpable. The presence of ascites could not be determined. The urine contained large amounts of albumin, hyaline and granular casts, and red blood-corpuscles.

The blood-pressure was 166 systolic, and 110 diastolic. The blood chemistry on March 5th, was as follows: total non-protein nitrogen, 70 mg. per 100 c.c.; urea nitrogen, 59; uric acid, 5; and creatinin, 3.1. The urinary output for the first twenty-four hours was 420 c.c. The Wassermann test was negative.

He was given nothing to eat and drink for the first twenty-four hours. He was then put on a diet of white bread, salt-free butter, potatoes, cream,

sugar, fruits, and vegetables, the total daily calories not exceeding 1500. The total fluid intake was limited to 500 c.c. in twenty-four hours.

He was given tincture of digitalis, 2 c.c., every four hours for the following two days. On the evening of the first day he complained of severe headache, was very restless, and his blood-pressure was found to be 210 systolic and 140 diastolic. He was given 1 gm. of chloral hydrate with 2 gm. of sodium bromid immediately, and 0.5 gm. of chloral every four hours. There were no convulsions. The chloral was discontinued on March 8th, when his blood-pressure was found to be 144 systolic and 78 diastolic. The edema had disappeared from the face, legs, and feet, and was only present to a slight degree in the scrotum and over the sacral region.

The blood chemistry on March 8th was as follows: total non-protein nitrogen, 44 mg. per 100 c.c.; urea nitrogen, 32; uric acid, 3.5; creatinin, 3.1. The urinary output had increased to over 1800 c.c. on that day. The fluid intake was increased to 800 c.c. He continued to improve. The blood-pressure on March 11th, was 124 systolic and 80 diastolic, and remained around these figures. The edema had completely disappeared. The blood chemistry on March 15th, was: total non-protein nitrogen, 32 mg. per 100 c.c.; urea nitrogen, 18; uric acid, 2.3; creatinin, 1.5. The urine still contained considerable amount of albumin but no red blood-corpuscles.

More protein was now added to his diet and the fluid intake increased gradually to 1500 c.c. He was kept in bed until April 6th, and discharged ten days later. At the time of his discharge his blood-pressure was 120 systolic and 84 diastolic, and his urine contained a faint trace of albumin.

The Treatment of Anuria.—The presence of anuria with acute diffuse glomerulonephritis is evidence of the extreme degree of obstruction to the flow of blood through the glomeruli. The means of treatment are therefore those which we have already mentioned: the limitation of food and fluid intake, venesection, hot baths, occasional hot packs, the application of heat to the kidney region. Especially beneficial is Volhard's fasting cure. Volhard also recommends after a few days of fasting the single administration of a large amount of water (1500 c.c.) in an attempt to produce a release of the spastic contraction of the arteries in the kidneys.

Decapsulation of the kidneys has been repeatedly carried out by many surgeons. The subject has been reviewed recently by Volhard,[1] Hartwich,[2] and by J. and W. Israel.[3] These observers have found decapsulation of the kidneys of benefit in the anuria of acute diffuse glomerulonephritis, but of no value in the anuria of bichlorid of mercury poisoning. If the anuria in the course of acute diffuse glomerulonephritis persists in spite of medical

treatment for three or four days, decapsulation of the kidneys is indicated. One should remember, however, that diuresis occasionally sets in spontaneously following an anuria of three or four days duration and even longer.

Volhard[1] considers the possibility, that in addition to the local effect of decapsulation on the kidneys, the effect of the aseptic operation is to produce certain changes in the blood which might act in the manner of non-specific irritation therapy. He explains in a similar manner the result of *x*-ray radiation to the kidney region in anuria, and cites a case of Stephan in which the *x*-ray radiation was followed by increased diuresis.

What we have said concerning the anuria also holds good for those cases in which the urine production is not totally suppressed, but in which the amount of urine is so small that the danger of true uremia is almost the same as in anuria.

CONCLUSION

With the above mentioned principles to guide us, the problems of treatment in the individual case of acute diffuse glomerulonephritis are considerably simplified.

The most valuable means of treatment at the beginning and at the height of the disease is the rigid limitation of the food and fluid intake. This should be preceded whenever possible by the total deprivation of food and fluid for a period of one to two days.

Convulsions in this disease can be prevented by abstinence from food and fluid, and by the judicious use of chloral hydrate and of morphin.

The prevention and the treatment of cardiac failure is of prime importance.

Rest in bed should be enforced throughout the acute stage of the disease.

In the treatment of the anuria of this disease, decapsulation of the kidneys should be considered after other means have been tried for three to four days.

The use of the *x*-ray in the treatment of anuria and in the treatment of the severe cases of acute diffuse glomerulonephritis is a subject for future investigation.

Other forms of non-specific irritation therapy may prove useful.

The treatment of embolic glomerulonephritis is included in that of subacute bacterial endocarditis.

The treatment of the non-embolic focal glomerulonephritis should be directed toward the disease which it complicates, and in the chronic cases toward the eradication of foci of infection in the teeth, tonsils, and accessory sinuses of the nose.

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SCHONLEIN-HENOCH'S PURPURA. REPORT OF A CASE WITH REVIEW OF THE LITERATURE

THE association of purpura with joint symptoms and gastro-intestinal crises has long been recognized as a clinical entity and studied under various names. The following case of purpura in a man aged fifty-two is considered interesting because of the severe gastro-intestinal complications, and because the occurrence at that age is unusual.

Case Report.—C. B., male, aged fifty-two, was admitted to the Fifth Avenue Hospital July 15, 1927. Four months previously he began to have attacks of epigastric pain, usually after meals, without nausea or vomiting. During this time he was constipated and employed cathartics frequently. Ten days before admission he began to have some swelling and pain in the left knee. Five days later he complained of pain and swelling in the left ankle, and a bluish purplish eruption appeared on the inner surface of both legs. Pain in the joints became so severe that he was forced to bed. The family history was essentially negative. The past history was unimportant except for frequent attacks of bronchitis and sore throat. Fourteen years ago a herniotomy was performed. He had lost some weight without knowing how much.

The pertinent findings in the physical examination were: weight 124 pounds, considerably undernourished; tongue heavily coated; anterior cervical glands palpable on both sides. Percussion note was impaired over the right upper lobe where breathing was bronchovesicular in character; scattered rhonchi audible over the entire chest. The abdomen was flaccid and tender over its lower half. The left knee, ankle, and foot were moderately swollen and tender. On the inner surface of both legs there were numerous spots, pin-point in size, ranging in color from red to blue. Similar spots were visible over the popliteal regions and on the anterior surface of both thighs. These did not disappear on pressure and were not elevated above the skin level.

Clinical Course.—Two days after admission he began to vomit after meals and complained of abdominal pains of a colicky nature. The vomiting grew worse and persisted to the end, but at no time was it fecal in character.

During the first five days there were several bowel movements, but subsequently he had frequent discharges of brownish stringy liquid only. Nine days after admission the abdomen became moderately tympanitic, his condition became critical, and the next day while being transfused, he died.

After one week in the hospital the joint edema and pain disappeared, but there was no appreciable change in the purpuric eruption. The temperature on admission was 99.2° F., and did not rise above 100.4° F. throughout the entire time.

Laboratory Data.—Blood-count (July 16th): Hemoglobin 58 per cent., red blood-cells 4,000,000 per cubic millimeter, white blood-cells 5500 per cubic millimeter, polymorphoneutrophils 72 per cent., lymphocytes 26 per cent., transitionals 1 per cent., eosinophils 1 per cent., platelets 200,000 per cubic millimeter. Another blood-count done July 23d showed hemoglobin 60 per cent., red blood-cells 3,300,000, white blood-cells 7,200, polymorphoneutrophils 88 per cent., lymphocytes 11 per cent., eosinophils 1 per cent., platelets 275,000, no abnormal forms. Fragility determination of the erythrocytes—hemolysis begins at 0.475 and is complete at 0.325. Blood Wassermann test—negative. Stool and vomitus—positive for occult blood. Sputum—negative for tubercle bacilli on three occasions. Urine—negative except for very faint trace of albumin. *x*-Ray of left ankle showed no bone or joint pathology. A gastro-intestinal series begun July 21st showed some gastric retention at the end of six hours; at the end of two hours the barium meal was scattered throughout the upper part of the small intestine, and the coils of the jejunum were dilated. After six hours the meal had not yet reached the cecum, and the intestinal coils were generally dilated. At twenty-four hours the cecum was filled and the dilatation persisted. After forty-eight hours the colon was filled and the dilatation of the small intestine was fairly uniform throughout. Above the pelvic brim in the mid-line there was an area suggesting partial obstruction.

Autopsy (by Dr. D. S. D. Jessup).—The abdomen contains a considerable amount of clear, light red serum, and the intestinal coils are matted together by adhesions. On separating the loops of small intestine, an abscess cavity containing foul smelling yellow pus is seen in the right lumbar region. The intestines in this region are so soft and necrotic that it is difficult to separate them without tearing. On the opposite side of the abdomen there are fresh lymph and sanguinous exudate, with marked congestion of the large and small intestines. Fifteen cm. above the cecum, the ascending colon shows an ulcer 3 cm. in diameter with a black hemorrhagic base. In the cecum there is a small perforation surrounded by a dark zone, adjacent to which is another hemorrhagic ulcer. A similar ulcer is seen in the small intestine about 1 meter from the ileocecal valve. Microscopic examination: The wall of the colon near the site of the ulceration shows loss of glands and some round cell infiltration. The floor of the ulcer shows infiltration with polynuclear, small mononuclear, and plasma cells. There are many pigmented cells in the mucosa of the adjacent intestinal wall which appear to be phagocytes. Portions of the wall of the small intestine show necrosis of the serosa and intense inflammatory infiltration of the muscularis and submucosa. The mucosa of the appendix shows pigmented cells, but there are no inflammatory changes.

Analysis of the Clinical Syndrome.—The mode of onset of this disease is variable. Frequently it begins with malaise, anorexia, and a mild pyrexia, but purpura, joint pains, or gastro-intestinal symptoms may usher in the attack. The temperature is generally not very high. Albuminuria and hematuria may occur with the onset, or at any time during the course of the illness. The duration of a single attack varies from one to ten days, although longer periods are also described. Generally, however, relapses occur which may come in succession after a very short interval of freedom, or are observed at irregular intervals over a period of many months or years.

Skin Lesions.—Osler[1] stresses the pleomorphic character of the skin lesions and divides them into four main groups: (1) Purpura—all varieties; (2) effusion—urticarial wheals and angioneurotic edemas; (3) erythema with or without swelling resembling erythema multiforme, or even erythema nodosum; (4) necrotic areas which may result when a localized infiltration of blood and serum is very intense, and bullæ form with necrosis of the superficial layer of the skin. Any one, or all, or various combinations of these skin eruptions may be present in the same patient during any one attack, or in the same individual over a period of many years the skin lesions may differ in the different attacks. Purpura need not be a prominent feature, and in fact, may be absent entirely. Pruritus is common. Frequently there are no skin manifestations and the diagnosis must be made on the basis of the joint and abdominal complications. According to Frank,[2] the skin is sensitive to intradermal injection of substances such as tuberculin, which will produce extensive hemorrhagic infiltrations with necrotic centers. The tourniquet test is positive, but whereas in purpura hemorrhagica it will produce a crop of large purpuric areas and extensive ecchymoses, in the type of purpura under discussion only a small petechial eruption results.

Gastro-intestinal Lesions.—The symptoms referred to the gastro-intestinal tract consist of colicky pains, vomiting and diarrhea, with blood and mucus in the stools. Occasionally the vomitus may be sanguinous, and constipation may precede the

diarrhea. As a rule, the prognosis is favorable, and the symptoms disappear when the attack is over. But, as in the case here described, more serious complications may supervene. Partial or complete intestinal obstruction has followed, and a suppurative peritonitis may result from perforation of the bowel wall. The clinical picture sometimes simulates intussusception, but actual intussusception does occur.[3] The failure to make a correct diagnosis has led to useless laparotomies, and as a result, both surgeon and internist have adopted a conservative point of view as regards surgical intervention. However, it should be kept in mind that surgery is sometimes indicated and may be a life-saving measure, as in order to reduce an intussusception or to resect a necrotic piece of intestine.

The anatomic changes, of which Sutherland gives an excellent account,[4] correspond to those seen in the skin; serous exudate, edema, hemorrhage, and in the more severe instances, necrosis, These occur in any or all the layers of the bowel wall which will be found deeply congested or hemorrhagic, with a leathery feel. Scattered purpuric spots are found on the mesentery, the serosa, or mucosa. Superficial ulcers due to sloughing at the site of the hemorrhage are not infrequent, but extensive ulcerations due to profuse hemorrhage into the wall of the gut have been described. If the hemorrhage is of sufficient amount, it will produce paralysis in the region affected, and either partial or complete obstruction will ensue. The increased peristalsis in the adjacent portion of the bowel may drive it into the paralyzed part, and thus produce intussusception.

The site of election for these lesions seems to be the terminal ileum, but any part of the gastro-intestinal canal may be involved. In the literature reviewed there is no mention of any case with esophageal complications. Morris[5] cites a case in which a stomach tube brought up a small piece of gastric tissue, which grossly and microscopically showed profound edema. Silbermann[6] reports a case where at autopsy a small perforation of the stomach wall was found. Nobecourt[7] describes a case which on postmortem examination showed general suppurative peritonitis, congestion of the stomach, engorgement of the

lower end of the ileum, and a small perforation in the duodenum. In Zimmermann's case[8] of a woman aged forty-six, the autopsy showed multiple necrotic areas in the ileum, lower jejunum, and descending colon—a real necrotic enterocolitis. Likewise, the rectal mucosa was edematous and undergoing grayish discoloration. Nobecourt[7] and Jacobson[9] report typical cases where operation revealed a true hemorrhagic appendix.

Joint Symptoms.—Pain, swelling, and tenderness are the essential features. Several joints are usually affected, especially the knees and ankles, but any of the joints may be involved, simultaneously or in succession. As a rule no bony changes are found, but the counterpart of the skin and gastro-intestinal lesions are to be found here. There may be hemorrhage into the joint capsule, synovial membranes, periosteum and muscle sheaths. On the other hand, the conditions near the joints may be due to the localized infiltration of the overlying skin. Extensive hemarthrosis is rare.

Kidney Symptoms.—These offer the most serious complications. Albuminuria, hematuria, and true glomerulonephritis are found. According to Osler, the renal lesions may be divided into three groups: (1) Those in which the albuminuria shortly disappears and the condition clears up; (2) those which run an acute course and terminate in dropsy and uremia; and (3) those in which the nephritis becomes chronic with secondary cardio-vascular changes.

Hematology.—There is nothing especially characteristic of the blood picture in this disease. Occasionally there is a moderate anemia, but the character of the erythrocytes is unchanged. Glanzmann,[10] and Pfaundler and von Seht[11] report slight leukocytosis, a moderate eosinophilia, and occasionally a shift to the left according to Arneth's classification. The number of blood-platelets is usually normal, may be increased, or somewhat reduced. Bleeding and coagulation time are within normal limits, and the clot retraction is normal.

Age and Sex.—This disease occurs most frequently in young females. It is very rare under three years and most common in the second decade. Von Dusch and Hoche[12] report a series of

44 cases ranging in age from three to forty-six years. They were not aware of any cases under three or over forty-six. In Pratt's series of 43 cases,[13] the youngest was four, the oldest forty-seven, and only 4 occurred in the fourth decade. Of a series of 150 cases reviewed by the author for this publication, there were 5 in the fifth decade.

Historic Review.—The form of purpura discussed in this paper is generally associated with the names of Schönlein and Henoch, but a perusal of the available literature brings to light a number of excellent descriptions of this condition which antedate both of these men. Thus, Willan[14] (1808) describes a case of purpura occurring in a woman aged thirty-six, who ran a course of abdominal colic, vomiting, bloody diarrhea, painful and swollen joints, and a variety of skin lesions including purpura, urticarial wheals, and angioneurotic edema. Bateman[15] (1819) in his description of purpura simplex mentions pain in the limbs as a prominent symptom. Likewise, in purpura urticans he finds "some edema of the extremities usually accompanies it, and it is occasionally preceded by a stiffness and weight of the limbs." Ollivier d'Angers[16] (1827) goes a step further. After describing a typical case he makes a differential diagnosis from purpura hemorrhagica of Werlhof. In the latter condition hemorrhages from the mucous membranes are very frequent. There are no gastro-intestinal symptoms, and the skin shows no urticarial or edematous lesions. Latour[17] (1828), Rehfeld[18] (1838), Vallin[19] (1863), Wagner[20] (1869), Vernier[21] (1873), and Jones[22] (1873) report additional cases belonging to this group.

To Schönlein[23] (about 1830) goes the credit for emphasizing the joint symptoms. Under the name of peliosis rheumatica, he describes a disease characterized by painful, tender and swollen joints, associated with purpura chiefly on the extremities, and warns against confusing it with purpura hemorrhagica.

Henoch's contribution consists in reviving interest in this condition as a distinct entity, and in further elucidating the gastro-intestinal complications. In 1874, Henoch[24] reports 4 cases of purpura in which in addition to the joint pains and

swellings, and the purpuric eruption, vomiting, colic, and diarrhea are prominent features. Henoch, like Schönlein, also differentiates between this type of purpura and purpura hemorrhagica. At a later date[25] he observes the presence of hematuria and nephritis, and draws a fairly complete clinical picture of this disease as we know it today.

Subsequently the literature affords numerous observations by various authors, but not all of them follow the teachings of Schönlein and Henoch. There appear at least two separate schools, the first placing all the purpuras in one group, and the other differentiating the Schönlein-Henoch syndrome as a distinct disease entity. Thus Scheby-Buch[26] and Koch[27] make the assertion that purpura simplex, rheumatica, and hemorrhagica may be considered variants of the same hemorrhagic diathesis, and belong together etiologically. Abdominal and joint symptoms may complicate any member of this group. Biedert and Vogel[28] conclude that purpura hemorrhagica is a more serious form of either purpura simplex or peliosis rheumatica. A similar opinion is expressed by Baginsky[29] and Litten.[30]

Opposing the former point of view, von Dusch and Hoche[12] follow in the steps of Henoch and differentiate clinically between purpura hemorrhagica and the Schönlein-Henoch forms. In the same school we may place Marfan,[31] Lenoble,[32] Hutinel,[33] and Krauss.[34] Interesting is the view of Leloir[35] who distinguishes two types: "Purpura par modifications du sang" and "purpura par modification des vaisseaux." Brohm (1881) and Krauss (1883) were the first to observe a reduction in blood-platelets in purpura hemorrhagica, a condition which did not exist in Schönlein-Henoch's purpura, but the significance of this phenomenon, the recognition of which establishes a definite turning point in the conception of purpura, was not realized at that time. Further contributions to the hematology of purpura hemorrhagica were made by Denys (1887), who reports a normal clotting time, by Hayem (1895) who describes the irretractility of the clot and by Duke (1910–1912) who observes the increase in bleeding time.

Duke also emphasizes the importance of a very low platelet

count in the diagnosis of purpura hemorrhagica, but it was left to Frank[36] to conclude (1915) that this reduction in the platelets is not only an essential feature of purpura hemorrhagica, but is the cardinal point about which the entire symptomatology hinges. Likewise this thrombopenia is the main hematologic difference between purpura hemorrhagica and Schönlein-Henoch's purpura. Leschke[37] accepts Frank's suggestion and divides the purpuras into two main groups: (1) Thrombopenic purpura, and (2) non-thrombopenic purpura which includes Schönlein-Henoch's purpura. However, this attitude is not shared by other investigators. Naegli[38] recognizes that thrombopenia may or may not accompany purpura, but that a classification cannot be made strictly on either a morphologic or clinical basis. Morawitz[39] admits that purpura hemorrhagica and Schönlein-Henoch's purpura may be isolated as clinical entities, but that all purpuras cannot be grouped under these two headings. Thrombopenia is only a symptom and may occur in numerous conditions.

Pathogenesis.—In his work with the capillariscope Müller[40] observes the skin capillaries in a case of Schönlein-Henoch's purpura, and finds the capillaries dilated, lengthened and partially distorted. This condition he does not find in purpura hemorrhagica. Apparently unlike purpura hemorrhagica we are dealing here with a condition that profoundly affects the blood-capillaries, and not with a true hemorrhagic disease. According to Frank[2] (1925) this is a transudative-exudative diathesis with facultative hemorrhagic character, and the purpura is only a secondary manifestation which develops in a primary erythematous or urticarial lesion. The basis of the lesions whether in the skin, alimentary canal, kidneys or joints is a universal affection of the capillaries, which produces all the transitional stages between hyperemia and edema, and true inflammatory processes. Thus, we encounter not only melena, but a true colitis with mucosanguinous stools; not merely a hematuria, but a real hemorrhagic nephritis.

The effect of capillary poisons, such as histamin, on the capillary mechanism has been studied by Dale and Laidlaw.[41]

The latter injected a cat intravenously with histamin, and produced capillary lesions analogous to those mentioned previously. They conclude that histamin produces a condition resembling either traumatic or anaphylactic shock, with marked accumulation of blood in the peripheral capillaries, and an increase in the viscosity of the blood due to leakage of the plasma from the capillaries into the tissues. This stasis of blood in the capillaries results from dilatation due to changes in the colloidal chemistry of the capillary endothelium, which changes may also account for rendering the endothelium more permeable to plasma, and if carried still further, for a diapedesis of cellular elements as well.

Dale and Laidlaw further observe that this state of affairs resembles a process which, if it occurred locally, would produce a set of phenomena seen in inflammation, *i. e.*, widening of the capillary lumen, tendency to stasis and transudation of plasma. Actually, histamin when locally injected produces swelling, redness and urticarial wheals. The author made an intradermal injection of 0.0001 gm. of histamin in the forearm of a severe asthmatic. Within two minutes there appeared an urticarial wheal 3 cm. in diameter, surrounded by an area of hyperemia which involved two-thirds of the flexor surface of the forearm. The rest of the forearm, the dorsal surface of the hand, and a large part of the arm presented an irregular red mottling, which on close inspection, showed marked prominence and dilatation of the superficial skin vessels. A similar condition was seen on portions of the other arm.

Whereas with histamin we may experimentally produce lesions similar to those seen in Schönlein-Henoch's disease, in serum sickness we have an opportunity of observing clinically a very similar picture. Urticaria, angioneurotic edema, erythema, abdominal colic, vomiting, diarrhea and albuminuria are seen in both groups. Purpura is not common in serum sickness, yet there are instances in the literature, such as Widmer reports,[42] where purpura follows the administration of horse-serum. Widmer[43] likewise reports a series of cases where the administration of diphtheria antitoxin was followed by catarrhal,

membranous or hemorrhagic enteritis. Several cases of food allergy associated with purpura are reported by Alexander and Eyermann[44] in which, although there were no positive skin reactions to an offending allergen, removal of certain articles of food from the dietary resulted in cure of the symptoms.

On the basis of evidence similar to that just presented, Glanzmann[10] concludes that Schönlein-Henoch's purpura is an anaphylactic phenomenon. This results from the introduction of a foreign protein into the system which induces changes in the blood-plasma constituents sufficient to liberate an anaphylatoxin, which acts as a capillary poison by affecting the vasomotor mechanism. The foreign protein is derived from a bacterial infection, and therefore, according to Glanzmann, Schönlein-Henoch's purpura is infectious in origin, and associated either with some known or unknown infectious process.

Unquestionably there are instances of purpura which fit this category, but to make a sweeping generalization for the entire group seems ungrounded in fact. It is more reasonable to assume that since a derangement in the capillary mechanism is the underlying pathology, any thing which can produce this derangement may call forth the syndrome. Among the etiologic factors, therefore, we would enumerate the following: (1) Anaphylatoxin associated with a bacterial protein; (2) food allergy; (3) histamin or histamin-like substances which may originate in the gastro-intestinal tract as a result of the elaboration of toxic aminobases from the protein molecule. It still remains to be solved whether the action is primary on the capillary endothelium, or whether the vasomotor mechanism is first affected. Müller believes that the primary lesion is in the vasomotor system, and classifies this type of purpura under the vasoneuroses, and Castex[45] reports definite changes in the sympathetic nuclei.

Differential Diagnosis.—Schönlein-Henoch's purpura may be differentiated from purpura hemorrhagica both hematologically and on the basis of the clinical picture.*

* After Frank, Glanzmann, and Pfaundler and von Seht.

	Schönlein-Henoch	*Purpura hemorrhagica*
Constitutional symptoms:	Malaise, headache, anorexia, coated tongue, fever.	Few; no fever unless secondarily as result of complicating infection or profound anemia.
Special features:	Urticaria, erythema, edema, joint pains and swelling; abdominal colic, vomiting, melena, hemorrhagic nephritis.	Absent; melena without colic and hematuria without nephritis do occur.
Skin lesions:	Petechiæ, purpura, urticaria, erythema.	Ecchymosis, extensive suggilations, purpura.
Localization:	Extremities preferred especially near the joints; head usually spared.	Irregular, frequently on head.
Mucous membrane hemorrhages:	Moderate bleeding from gastro-intestinal tract, otherwise rare.	Frequent epistaxis, stomatorrhea; uterine, vesical, gastro-intestinal and renal bleeding may be extensive.
Bleeding time:	Normal.	Increased.
Clotting time:	Normal.	Normal.
Clot:	Retractile.	Non-retractile.
Morphology of blood:	Slight leukocytosis; occasional eosinophilia.	Tendency to leukopenia and relative lymphocytosis.
Platelets:	Generally normal, may be increased or moderately diminished.	Marked thrombopenia with giant forms.
Tourniquet test:	Positive.	Very strongly positive with large ecchymoses.

Conclusions.—1. Schönlein-Henoch's purpura is a definite clinical and pathologic entity.

2. The disease is characterized pathologically by an injury to the capillary motor mechanism.

3. In this respect it is related to a large group of anaphylactoid disorders, such as serum sickness, food allergy, angioneurotic edema and urticaria, but allowing for individual variations the name is best reserved for the classic combination of skin lesions with gastro-intestinal, joint, and kidney symptoms.

4. The etiologic factors are variable and are characterized by their ability to affect the capillaries. Non-specific bacterial infection, autogenous capillary poisons, such as histamin, and food sensitization are suggested as possibilities.

5. The prognosis is generally favorable, but the gastro-intestinal and renal complications may prove serious and even fatal.

6. The gastro-intestinal lesions may be of such nature as to warrant surgical intervention.

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